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(54) Pharmaceutical preparations based on gastrointestinal mucosa-adherent matrixes or coatings

Auf der gastrointestinale Mukosa klebenden Matrizen oder Überzugmitteln enthaltende pharmazeutische Zubereitung

Préparations pharmaceutiques à base de matrices ou d'enrobages adhérents à la muqueux gastrointestinale

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(73) Proprietor: **TAKEDA CHEMICAL INDUSTRIES, LTD.**
Chuo-ku, Osaka 541 (JP)

(72) Inventors:
- **Akiyama, Yohko**
  Ibaraki, Osaka 567 (JP)
- **Hirai, Shin-ichiro,**
  201, Tamamoto-cho
  Shimogyo-ku, Kyoto 600 (JP)
- **Nagahara, Naoki**
  Amagasaki, Hyogo 661 (JP)

(74) Representative: **Lewin, John Harvey et al**
Elkington and Fife,
Prospect House,
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

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Description

FIELD OF THE INVENTION

The present invention relates to a gastrointestinal mucosa-adherent matrix adapted to stay long in the gastrointestinal tract for sustained drug release, a solid pharmaceutical preparation based on the matrix, and a coating composition which renders matrix-based dosage forms of a solid pharmaceutical preparation adherent to the gastrointestinal mucosa.

BACKGROUND OF THE INVENTION

Controlled-release drug delivery systems, particularly sustained-release preparations, are advantageous in that they help to reduce the frequency of administration of a drug without detracting from the effect of medication, prevent any sudden elevation of the blood concentration of the drug to reduce the risk of side effects, and maintain a therapeutically effective blood concentration for an extended period of time. Therefore, much research has been undertaken in the field of controlled release technology from the aspects of active drug formulation and dosage form. By way of illustration, there are known an encapsulated preparation such that a core containing an active ingredient is covered with a shell, and a matrix-type preparation such that an active ingredient has been dispersed in a release-controlling layer. These preparations are generally provided in such dosage forms as tablets, capsules and granules, for example.

Meanwhile, many drug substances are absorbed mostly from the small intestine and, to a lesser extent, from the large intestine. Moreover, in humans, reportedly it takes about 5 to 6 hours for an orally administered drug to reach the large intestine.

However, in oral administration, the residence time of the drug in the digestive canal is of necessity limited even if its release is critically controlled by a sophisticated controlled release system, so that the drug is not efficiently absorbed but is excreted from the body without being fully utilized. Furthermore, in the case of a drug substance which acts directly and locally to produce the expected effect, it is likewise excreted without being utilized if the duration of contact is short. In particular, in cases where the drug substance is sparingly soluble, its pharmacological actions cannot be effectively utilized. Therefore, in conventional drug delivery systems, it is difficult to ensure absorption of active ingredients beyond a limited time period.

European Patent Publication No. 0368247A3 discloses a matrix preparation such that a pharmaceutically active ingredient is dispersed in a polyglycerol fatty acid ester-based matrix which is solid at ambient temperature. Moreover, European Patent Publication No. 0406856A2 discloses an FGF protein composition which is a granulated preparation using a polyglycerol fatty acid ester. Furthermore, European Patent Publication No. 0455391 proposes a granulated preparation prepared by thermal fluidization of a particulate composition containing a granular polyglycerol fatty ester having a melting point of 40 to 80°C and an active ingredient.

However, none of these prior art proposals in the patent literature teaches or suggests a pharmaceutical preparation having a gastrointestinal mucosa-adherent property.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a gastrointestinal mucosa-adherent matrix adapted to attach itself to the gastrointestinal mucosa to thereby stay long within the gastrointestinal tract, and to promote absorption of the active ingredient for improved bioavailability.

It is another object of the invention to provide a gastrointestinal mucosa-adherent matrix adapted to attach itself to a specific site within the gastrointestinal tract to thereby allow an active ingredient to act directly on the living body.

It is still another object of the invention to provide a gastrointestinal mucosa-adherent matrix which allows even a sparingly water-soluble active ingredient to be effectively utilized by the body.

A further object of the invention is to provide a pharmaceutical preparation having the above-mentioned beneficial characteristics.

Yet another yet object of the invention is to provide a coating composition which renders a drug substance or dosage form adherent to the gastrointestinal mucosa.

The inventors of the present invention found that the duration of action of various active ingredients can be prolonged by incorporating a certain substance having the property of becoming viscous on contact with water (hereinafter referred to as a "viscogenic agent") in a pharmaceutical composition, and, optionally, additionally coating the pharmaceutical composition with such a viscogenic agent. The present invention has been completed on the basis of these findings.

Thus, the present invention provides a gastrointestinal mucosa-adherent matrix which is solid at ambient temperature, and which comprises a viscogenic agent as defined below dispersed at least in the neighbourhood of the surface layer of a matrix particle containing a polyglycerol fatty acid ester and/or a lipid as also defined below and an active

ingredient.

The gastrointestinal mucosa-adherent matrix as just defined may, optionally, also have on each matrix particle a coating layer comprising a viscogenic agent as defined below.

According to one aspect of the present invention, there is provided a gastrointestinal mucosa-adherent matrix which is solid at ambient temperature, and which comprises (i) an active ingredient; (ii) a polyglycerol fatty acid ester and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (iii) a viscogenic agent having the property of becoming viscous on contact with water and selected from (a) acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers, in which matrix said viscogenic agent is dispersed at least in the neighbourhood of the surface layer of each matrix particle, and, optionally, said matrix particle additionally has a coating layer formed from a coating composition containing said viscogenic agent.

According to another aspect of the invention, there is provided a matrix coating composition for rendering matrix-based dosage forms of a solid pharmaceutical composition adherent to the gastrointestinal mucosa, which coating composition comprises (A) at least one polyglycerol fatty acid ester (PGEF) and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (B) at least one viscogenic agent having the property of becoming viscous on contact with water and selected from acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers.

The present invention also provides a solid pharmaceutical preparation based on the matrix, which may be in the form of fine granules or granules.

The present invention further provides the use of a coating composition as defined above to coat the particles of a gastrointestinal mucosa-adherent matrix as also defined above.

As used throughout this specification, the term "gastrointestinal mucosa-adherent" refers to any and all cases in which the property of adhering to the gastrointestinal mucosa is exhibited or imparted by the viscogenic agent, including cases in which the matrix additionally has an enteric or gastric coating layer which does not contain the viscogenic agent. The term "the neighbourhood of the surface layer" means not only the surface of the matrix particle but also the region adjoining the surface, including a coating layer such as that mentioned just above.

The term "coating" is used herein to mean not only a process in which the whole surface of a matrix particle is covered with a coating composition containing the viscogenic agent but also a process in which the surface of the matrix particle is partially covered with such a coating composition.

It should also be understood that, where the matrix and/or the polyglycerol fatty acid ester or the lipid is a mixture, the composition does not show a distinct melting point but softens at a specific temperature. The term "melting point" as used in this specification includes the softening point displayed by such a mixture.

DETAILED DESCRIPTION OF THE INVENTION

The viscogenic agent used in the present invention is a substance as defined above which develops a sufficient degree of viscosity in the presence of water to adhere to the gastrointestinal mucosa and is pharmaceutically acceptable. Preferred species of the viscogenic agent swell or gain in viscosity to a remarkable extent on contact with water. As examples of such viscogenic agent according to the invention, there may be mentioned (a) acrylic acid polymers having a molecular weight higher than 1,000,000 and not greater than 5,000,000 containing 58.0 to 63.0 percent by weight of carboxyl groups and salts of said acrylic acid polymers, (b) pectin, (c) tragacanth gum and (d) agar.

The preferable viscogenic agents are those having a viscosity in the range of 0.003 to 50 Pas (3 to 50,000 cps), preferably 0.01 to 30 Pas (10 to 30,000 cps), and, more preferably 0.015 to 30 Pas (15 to 30,000 cps), as a 2 percent by weight aqueous solution thereof at 20°C. When a polymer becomes viscous as a result of neutralization, the viscosity of 0.2 percent by weight of the aqueous solution of the viscogenic agent is, for example, in the range of 0.1 to 500 Pas (100 to 500,000 cps), preferably, 0.1 to 200 Pas (100 to 200,000 cps), and, more preferably, 15 to 100 Pas (1,500 to 100,000 cps) at 20°C. In the present invention, at least one of such viscogenic agents is employed, and needless to say, two or more species of said viscogenic agents may be employed in combination.

The acrylic acid polymers containing carboxyl groups or salts thereof as defined above include, for example, acrylic acid polymers obtainable by polymerization of a monomer containing acrylic acid and salts thereof as a monomer component. The salts may be the corresponding salts of monovalent metals such as sodium or potassium, for example, and of divalent metals such as magnesium or calcium, for example. Such acrylic acid polymers and salts contain 58.O to 63.O percent by weight of carboxyl groups and have molecular weights in the range of from above 1,000,000 to not greater than 5,000,000. The preferred acrylic polymers include an acrylic acid homopolymer or a salt thereof. Such polymers are described as carboxyvinyl polymers in the Formulary on Non-official Drugs (October, 1986). As specific examples of polymers in this category, there may be mentioned, for example, carbomers [Trade name: Carbopol™ (hereinafter referred to as Carbopol™), The B.F. Goodrich Company] 910, 934, 934P, 940, 941 and 1342 (NF XVII), for example, HIVISWAKO 103, 104, 105 (Trade name of Wako Pure Chemical Industries, Japan), NOVEON™ AAI (Trade name of The B.F. Goodrich Company), and Calcium Polycarbophil™ (USP XXII).

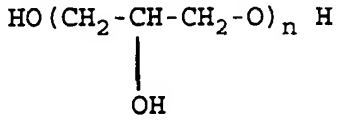
Additionally, the viscogenic agent of the invention may be, for example, agar, pectin or tragacanth gum.

Preferred viscogenic agents contain at least one of acrylic acid polymers and salts thereof. Particularly preferred viscogenic agents are acrylic acid polymers and salts thereof.

The polyglycerol fatty acid esters are esters of polyglycerols with fatty acids, and may be monoesters, diesters or polyesters. The polyglycerol fatty acid esters show no crystal polymorphism and are characterized in that they hardly interact with pharmacologically active ingredients. Therefore, the active ingredient in the presence of a polyglycerol fatty acid ester is little deactivated and remains stable for a long time.

Polyglycerol is a "polyhydric alcohol containing, in each molecule, n (cyclic form) to n + 2 (straight or branched form) hydroxyl groups and n - 1 (straight or branched form) to n (cyclic form) ether bonds" ["Polyglycerin Ester", edited by Sakamoto Yakuhin Kogyo Co., Ltd., Japan, published May 2, 1986, page 12].

A compound of the following formula (I), for instance, may be employed as a polyglycerol to form the polyglycerol fatty acid ester of the invention:



wherein n represents the degree of polymerization which is an integer of not less than 2.

In the above formula, n is generally 2 to 50, preferably, 2 to 20, and, more preferably, 2 to 10. The polyglycerols need not be straight-chain but may be branched.

Typical examples of such polyglycerols are diglycerol, triglycerol, tetraglycerol, pentaglycerol, hexaglycerol, heptaglycerol, octaglycerol, nonaglycerol, decaglycerol, pentadecaglycerol, eicosaglycerol and triacontaglycerol. Of these species of polyglycerol, tetraglycerol, hexaglycerol and decaglycerol are used most frequently.

The fatty acid includes, for example, saturated or unsaturated higher fatty acids containing 8 to 40 carbon atoms, preferably 12 to 22 carbon atoms. Thus, for example, palmitic acid, stearic acid, oleic acid, linolic acid, linolic acid, linolenic acid, myristic acid, lauric acid, ricinoleic acid, caprylic acid, capric acid and behenic acid may be mentioned. Among these fatty acids, for example, stearic acid, oleic acid, lauric acid, ricinoleic acid and behenic acid are preferred.

As specific examples of such polyglycerol fatty acid esters,there may be mentioned behenyl hexa(tetra) glyceride, caprylyl mono(deca)glyceride, caprylyl di(tri)glyceride, capryl di(tri)glyceride, lauryl mono(tetra)glyceride, lauryl mono(hexa)glyceride, lauryl mono(deca)glyceride, oleyl mono(tetra)glyceride, oleyl mono(hexa)glyceride, oleyl mono(deca)glyceride, oleyl di(tri)glyceride, oleyl di(tetra)glyceride, oleyl sesqui(deca)glyceride, oleyl penta(tetra)glyceride, oleyl penta(hexa)glyceride, oleyl deca(deca)glyceride, linolyl mono(hepta)glyceride, linolyl di(tri)glyceride, linolyl di(tetra)glyceride, linoliyl di(hexa)glyceride, stearyl mono(di)glyceride, stearyl mono(tetra)glyceride, stearyl mono(hexa)glyceride, stearyl mono(deca)glyceride, stearyl tri(tetra)glyceride, stearyl tri(hexa)glyceride, stearyl sesqui(hexa9glyceride, stearyl penta(tetra)glyceride, stearyl penta(hexa)glyceride, stearyl deca(deca)glyceride, palmityl mono(tetra)glyceride, palmityl mono(hexa)glyceride, palmityl mono(deca)glyceride, palmityl tri(tetra)glyceride, palmityl tri(hexa)glyceride, palmityl sesqui(hexa)glyceride, palmityl penta(tetra)glyceride, palmityl penta(hexa)glyceride and palmityl deca(deca)glyceride.

Preferred polyglycerol fatty acid esters include, for example, behenyl hexa(tetra)glyceride (e.g. Riken Vitamin Co., Ltd., Japan; Poem J-46B, etc.), stearyl penta(tetra)glyceride (e.g. Sakamoto Yakuhin Kogyo Co., Ltd., Japan; PS-310), stearyl mono(tetra)glyceride (e.g. Sakamoto Yakuhin Kogyo Co. Ltd., Japan; MS-310), stearyl penta(hexa)glyceride (e.g. Sakamoto Yakuhin Kogyo Co., Ltd., Japan; PS-500), stearyl sesqui(hexa) glyceride (e.g. Sakamoto Yakuhin Kogyo Co., Ltd., Japan; SS-500) and stearyl mono(deca)glyceride, as well as mixtures thereof.

These polyglycerol fatty acid esters may be used either singly or in combination.

The molecular weight of the polyglycerol fatty acid ester is generally from 200 to 5000, preferably, from 300 to 2000, and, more preferably, from 500 to 2000. The HLB (hydrophile-lipophile balance) number of the polyglycerol fatty acid esters is generally 1 to 22, preferably, 1 to 15, and, more preferably, 2 to 9. The HLB number may be adjusted by using two or more polyglycerol fatty acid esters having different HLB numbers in combination. By varying the HLB number of the polyglycerol fatty acid esters, the release and dissolution rates of the active ingredient can be controlled as desired.

While polyglycerol fatty acid esters can be selectively used according to the active ingredient, the viscogenic agent and the matrix form chosen, those which are solid at ambient temperature (about 15°C) are employed. The melting point of the polyglycerol fatty acid ester may, for example, be from 15 to 80°C, preferably, from 30 to 75°C, and, more preferably, from 45 to 75°C.

When two or more polyglycerol fatty acid esters are used as a mixture, one or more of the esters may be liquid, provided that the matrix is solid at ambient temperature.

The lipid as a constituent of the matrix is one having a melting point of 40 to 120°C, preferably 40 to 90°C.

The lipids of the invention are saturated fatty acids having from 14 to 22 carbon atoms (e.g. myristic acid, palmitic

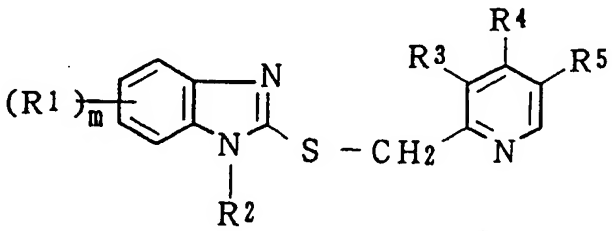
acid, stearic acid and behenic acid) and salts thereof (e.g. the corresponding sodium and potassium salts). Stearic acid is preferred.

There is no particular limitation on the type of active ingredient. The active ingredient in the present invention includes not only medicaments for human beings but also veterinary drugs. Thus, for example, central nervous system drugs such as antipyreticanalgestic-antiinflammatory agents, hypnotics and sedatives, antiepileptics, antivertigo agents and psychotropic agents; peripheral nervous system drugs such as skeletal muscle relaxants, autonomic drugs and antispasmodics; cardiovascular drugs such as cardiotonics, antiarrhythmic agents, diuretics, antihypertensive agents, vasodilators and vasoconstrictors; respiratory organ drugs such as bronchodilators and antitussives; digestive organ drugs such as antipeptic ulcer agents, digestants, intestinal function controlling agents and antacids; hormones; antihistaminics; metabolic drugs such as vitamins; antiulcer drugs; antibiotics; and chemotherapeutic agents may be mentioned by way of example.

Since the matrix composition of the present invention adheres to the gastrointestinal mucosa, a sparingly water-soluble active ingredient can be used effectively.

Among specific examples of the active ingredient are indomethacin, salicylic acid, trepibutone, amoxanox, aspirin, valproic acid, ketoprofen, ibuprofen, probenecid, 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid (hereinafter, AD-5467), isosorbide dinitrate, vinpocetine, estazoram, acetazolamide, papaverine, tolbutamide, acetohexamide, verapamil, quinidine, morphine, buprenorphine hydrochloride, dihydrocodeine phosphate, ephedrine, scopolamine, chlorpromagine, manidipine hydrochloride, phenylpropanolamine hydrochloride, chlorpheniramine maleate, phenylephrine hydrochloride, procainamide hydrochloride, sulfanylamide, molsidomine, sulfadiazine, diazepam, quinidine, N-ethyl-N-demethyl-8,9-anhydroerythromycin A 6,9-hemiketal, epinephrine, reserpine, acetaminophen, theophylline, caffeine, cefalexin, ampicillin, sulfisoxazole, delapril hydrochloride, ipriflavone, 2,2'-[(2-aminoethyl)imino]diethanol bis(butylcarbamate) dihydrochloride, cefotiam hexetil hydrochloride, cyclandelate, idebenone [namely, 2-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone], propranolol, haloperidol, chlorothiazide, hydrochlorothiazide, sucralfate, vitamins such as riboflavin, ascorbic acid, etc., minerals and amino acids.

Preferred examples of the active ingredient used in this invention include antiulcer agents and therapeutic agents for gastritis. Typical examples of such antiulcer agents include 2-[(2-pyridyl)methylthio] benzimidazole and its derivatives (hereinafter referred to briefly as benzimidazole compounds) and salts thereof. Among these benzimidazole compounds are the compounds described in Japanese Patent Publication No. 44473/1990 corresponding to United States Patent No. 4628098, Japanese Patent Publication No. 38247/1991, and Japanese Patent laid open No. 173817/1991 corresponding to United States Patent No. 5013743. To be specific, the compounds of the following formula (II) and physiologically acceptable salts thereof are particularly preferred:



(II)

wherein R^1 means hydrogen, an alkyl, a halogen, cyano, carboxy, an alkoxycarbonyl, an alkoxycarbonylalkyl, carbamoyl, a carbamoylalkyl, hydroxy, an alkoxy, a hydroxyalkyl, trifluoromethyl, an acyl, carbamoyloxy, nitro, an acyloxy, an aryl, an aryloxy, an alkylthio or an alkylsufinyl; R^2 means hydrogen, an alkyl, acyl, an alkoxycarbonyl, carbamoyl, an alkylcarbamoyl, a dialkylcarbamoyl, an alkylcarbonylmethyl, an alkoxycarbonylmethyl or an alkylsulfonyl; R^3 and R^5 may be the same or different and each means hydrogen, an alkyl, an alkoxy or an alkoxyalkoxy; R^4 means hydrogen, an alkyl, an alkoxy which may be fluorinated, an alkoxyalkoxy, an alkenyloxy which may be fluorinated or an alkynyloxy which may be fluorinated and m means an integer of 0 to 4.

The compound of the formula (II) can be produced by the processes described in the above patent literature or any process analogous thereto.

The substituents on the compound of the formula (II) are now briefly described.

Referring to R^1 in the above formula, said alkyl includes an alkyl group of 1 to 7 carbon atoms; the alkoxy of said alkoxycarbonyl includes an alkoxy group of 1 to 4 carbon atoms; the alkoxy of said alkoxycarbonylalkyl includes an alkoxy group of 1 to 4 carbon atoms and the alkyl thereof includes an alkyl group of 1 to 4 carbon atoms; the alkyl of said carbomoylalkyl includes an alkyl group of 1 to 4 carbon atoms; said alkoxy includes an alkoxy group of 1 to 5 carbon atoms; the alkyl of said hydroxyalkyl includes an alkyl group of 1 to 7 carbon atoms; said acyl includes an acyl group of 1 to 4 carbon atoms; the acyl of said acyloxy includes an acyl group of 1 to 4 carbon atoms; said aryl includes phenyl; the aryl of said aryloxy includes phenyl; the alkyl of said alkylthio includes an alkyl group of 1 to 6 carbon atoms; and

the alkyl of said alkylsulfinyl includes an alkyl group of 1 to 6 carbon atoms.

As represented by R^2, said alkyl includes an alkyl group of 1 to 5 carbon atoms; said acyl includes an acyl group of 1 to 4 carbon atoms; the alkoxy of said alkoxycarbonyl includes an alkoxy group of 1 to 4 carbon atoms; the alkyl of said alkylcarbamoyl includes an alkyl group of 1 to 4 carbon atoms; the alkyl of said dialkylcarbamoyl includes an alkyl group of 1 to 4 carbon atoms; the alkyl of said alkylcarbonylmethyl includes an alkyl group of 1 to 4 carbon atoms; the alkoxy of said alkoxycarbonylmethyl includes an alkoxy group of 1 to 4 carbon atoms; and the alkyl of said alkylsulfonyl includes an alkyl group of 1 to 4 carbons.

The alkyl group for R^3, R^4 and R^5 includes an alkyl group of 1 to 4 carbon atoms; the alkoxy includes an alkoxy group of 1 to 8 carbon atoms; and the alkoxy of said alkoxyalkoxy includes an alkoxy group of 1 to 4 carbon atoms.

Referring to R^4, the alkoxy of said alkoxy which may be fluorinated includes an alkoxy group of 1 to 8 carbon atoms, the alkenyl of said alkenyloxy which may be fluorinated includes an alkenyl group of 2 to 6 carbon atoms; and the alkynyl of said alkynyloxy which may be fluorinated inclides an alkynyl group of 2 to 6 carbon atoms. When the alkoxy, alkenyl or alkynyl group includes fluorinated, the preferred number of substitutions is 1 to 9.

The physiologically acceptable salts of the compound (II) include the corresponding hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, for example. These salts can be prepared from the compound of the formula (II) by the routine procedures.

The preferred substituents on the compound of the formula (II) are as follows. R^1 is hydrogen atom, fluorine atom, methoxy group or trifluoromethyl group and m=l. The substituent R^2 is hydrogen atom, R^3 is hydrogen atom or methyl group, R^4 is a C_{1-4} alkoxy group, a 2-propenyloxy group or an allyl group, which may be fluorinated, R^5 is hydrogen atom or methyl group. The preferred position of substitution for R^1 is position-4 or position-5 and preferably position-5.

Among compounds of the formula (II), the compounds in which R^1=R^2=R^5=H and R^3=H or CH_3 are preferred. Particularly preferred are compounds in which R^4 is a fluorinated C_{1-4} alkoxy group. The compounds in which R^1=R^2=R^5=H and R^3=CH_3 having the fluorinated $_{1-4}$ alkoxy group as R^4 include, among others, a compound having a 2,2,2-trifluoroethoxy as R^4 (hereinafter the compound may be referred to briefly as AG 1777), a compound having a 2,2,3,3-tetrafluoropropoxy as R^4 (hereinafter the compound may be referred to briefly as AG 1789), a compound having a 2,2,3,3,3-pentafluoropropoxy as R^4 (hereinafter the compound may be referred to briefly as AG 1776), a compound having a 2,2,3,3,4,4-hexafluorobutoxy as R^4, a compound having a 2,2,3,3,4,4,4-heptafluorobutoxy, and so on.

The benzimidazole compound of the formula (II), inclusive of a pharmacologically acceptable salt thereof, is a therapeutic drug for treatment of peptic ulcers which has gastric acid antisectretory activity, as a main pharmacological action, and gastric mucosa-protecting activity as well. By using the benzimidazole compound or salt in the matrix or solid preparation of the present invention, there can be obtained a more effective therapeutic regimen for peptic ulcers.

The active ingredient may be a peptide or a protein. Examples of such peptides and proteins include physiologically active peptides and hormones such as, for instance, insulin, vasopressin, interferons, IL-2, urokinase, serratiopeptidase, superoxide dismutase (SOD), thyrotropin releasing hormone (TRH), luteinizing hormone releasing hormone (LH-RH), corticotropin releasing hormone (CRF), growth hormone releasing hormone (GHRH), somatostatin, oxytosin and growth hormone; growth factors such as epidermal growth factor (EGF), nerve growth factor (NGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) (e.g. aFGF and bFGF), erythropoietin (EPO): calcitonin and colony stimulating factor (CSF) [bFGF includes rhbFGF muteins, such as CS23 (hereinafter referred to as TGP580 - European Patent Publication No. 281822)].

Due to their inherent properties, these active ingredients may vary in the solubility and the site of absorption within the gastrointestinal tract. Generally speaking, the solubility of basic drugs is high on the acidic side and low on the alkaline side. Therefore, the rate of release of a basic active ingredient in a matrix or preparation is fast in the stomach where the ingredient passes first and the environment is acidic, while it is slow in the intestine where the environment is neutral to weakly alkaline. Conversely, the solubility of an acidic drug is high on the alkaline side but low on the acidic side. Therefore, the rate of release of an acidic active ingredient in a matrix or preparation is fast in the intestine where neutral to weakly alkaline conditions prevail and slow in the stomach through which it passes in the first place.

Therefore, in order that an active ingredient may be released at a constant rate in both the stomach and the intestine, irrespective of environmental pH, the matrix containing a polyglycerol fatty acid ester or a lipid and which is solid at ambient temperature may contain a water-insoluble or sparingly water-soluble solid base together with an acidic active ingredient or an enteric polymer together with a basic active ingredient.

The acidic active ingredient includes various substances whose aqueous solutions, not in the form of salts, are acidic (e.g. pH 1.5 to 7.0, preferably, 2.0 to 6.8). Among such acidic active ingredients are, for example, indomethacin, salicylic acid, AD-5467, trepibutone, amoxanox, aspirin, valproic acid, ketoprofen, ibuprofen, ascorbic acid and probenecid. Among these acidic drugs, AD-5467, trepibutone and indomethacin are frequently used.

The solubility of the solid base in water may, for example, be not more than 0.1 g/ml, preferably not more than 0.001 g/ml, at 37°C. Solid bases of low solubility provide satisfactory results. As such solid bases, there may be mentioned the oxides, hydroxides, inorganic acid salts or organic acid salts of metals of Group I, II or III of the Periodic Table of the Elements, such as, for instance, magnesium oxide, magnesium hydroxide, magnesium silicate, magnesium carbonate, aluminum silicate, aluminum hydroxide, silicic acid (Syloid™, Aerosil™), magnesium metasilicate aluminate (Neusilin™),

magnesium stearate, calcium stearate, aluminum stearate and sodium stearate. These solid bases may be used singly or in combination.

The particle size of such solid base is generally not more than 50 μm and, preferably, from 0.05 to 20 μm. The proportional ratio of the solid base to the total preparation is generally from 1 to 80 percent by weight, preferably, from 1 to 50 percent by weight, and, more preferably, from 10 to 30 percent by weight.

The basic active ingredient includes various components whose aqueous solutions, not in the form of salts but in the free form, are basic (for example pH 7.O to 13.0, preferably, pH 7.O to 10.5). As such basic active ingredients, there may be mentioned, for instance, vinpocetine, estazoram, acetazolamide, papaverine, tolbutamide, acetohexamide, verapamil, quinidine, morphine, ephedrine, scopolamine, chlorpromagine and manidipine. Among these basic drugs, vinpocetine and acetazolamide are frequently employed.

The enteric polymer is a polymer which dissolves little in the stomach but dissolves in the intestine. Such enteric polymer is preferably an acidic polymer having a molecular weight of from 30,000 to 500,000, preferably from 70,000 to 400,000. As examples of such enteric polymer, there may be mentioned, for instance, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, carboxymethylethylcellulose (CMEC AQ™, Trade name of Kohjin Co., Ltd., Japan), methacrylic acidmethyl methacrylate copolymers (Eudragit™ L100-55, L100 and S100, Trade name of Röhm Pharma GmbH, Germany). These enteric polymers are used singly or in combination. Among these enteric polymers, Eudragit™ L100-55 is one of the polymers which can frequently be employed.

The enteric polymer is preferably used in finely divided form. The particle size of such enteric polymer is generally not more than, 50 μm and, preferably, from 0.05 to 10 μm. The content of such enteric polymer based on the total composition is generally from 1 to 80 percent by weight, preferably, from 1 to 50 percent by weight, and, more preferably, from 10 to 30 percent by weight.

The ratio of the content of the active ingredient to that of the entire matrix composition is from 0.0001 to 95 percent by weight, and, preferably, from 0.1 to 90 percent by weight.

The matrix according to the present invention may be classified into (A) a matrix composition such that the viscogenic agent has been dispersed at least in the neighbourhood of the surface layer of a matrix particle containing the active ingredient and the polyglycerol fatty acid ester, (B) a matrix composition such that the viscogenic agent has been dispersed in the neighbourhood of the surface layer of a matrix particle containing the active ingredient and the lipid, and (C) a matrix composition such that the matrix particle containing the viscogenic agent [(A) or (B)] has been additionally coated with a coating composition comprising or containing the viscogenic agent together with at least one component selected from polyglycerol fatty acid esters, enteric polymers and water-insoluble polymers.

The proportion of the polyglycerol fatty acid ester and/or lipid to be incorporated into each matrix particle is generally from 0.001 to 10,000 parts by weight, and, preferably, from, 0.001 to 50 parts by weight, relative to a part by weight of the active ingredient.

The matrix particles of matrices (A) and (C) each containing the polyglycerol fatty acid ester may give still more beneficial effects when a lipid is further incorporated. The lipid for this purpose is a pharmaceutically acceptable water-insoluble substance which is able to control the rate of dissolution of the active ingredient, such lipids being selected from C_{14-22} saturated fatty acids and salts thereof, as mentioned above.

When used in combination with the polyglycerol fatty acid ester, the lipid is used in a proportion which does not detract from the adhesiveness of the matrix to the gastrointestinal mucosa. In general, the lipid is used in a proportion of from 0.01 to 100 parts by weight and preferably from 1 to 20 parts by weight, relative to a part by weight of the active ingredient.

Unless contrary to the objects of the invention, various additives which are commonly used in the manufacture of solid pharmaceutical preparations, in particular, fine granules or granules, may be added to the particles of matrices (A), (B) and (C). The additives mentioned just above include, for instance, various excipients such as, e.g., lactose, corn starch, talc, crystalline cellulose (Avicel™), powdered sugar, magnesium stearate, mannitol, light silicic anhydride, magnesium carbonate, calcium carbonate and L-cysteine; binders such as, e.g., starch, cane sugar, gelatin, powdered gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, pullulan and dextrin; disintegrators such as, e.g., carboxymethylcellulose calcium, low-substituted hydroxypropylcellulose and croscarmellose sodium; surfactants including anionic surfactants such as, e.g., sodium alkylsulfates and nonionic surfactants such as e.g., polyoxyethylene-sorbitan fatty acid esters, polyoxyethylene-fatty acid esters and polyoxyethylene-castor oil derivatives; gastric antacids and mucosa-protecting agents such as, e.g., magnesium hydroxide, magnesium oxide, aluminum hydroxide, aluminum sulfate, magnesium metasilicate aluminate, magnesium silicate aluminate and sucralfate; colorants; corrigents; adsorbents; preservatives; wetting agents; antistatic agents and disintegration retarders. The amounts of these additives can be selected as desired within ranges which do not adversely affect the adhesion of the final preparation to the mucosa.

The gastrointestinal mucosa-adherent matrixes (A), (B) and (C) according to the invention are solid at ambient temperature. The preferred melting point of these matrixes may, for example, be from 30 to 120°C, and, preferably, from 40 to 120°C.

Referring to the matrices (A) and (B), the viscogenic agent is dispersed throughout each matrix particle containing

the polyglycerol fatty acid ester and/or lipid and the active ingredient, and may, optionally, be additionally dispersed in a coating film covering the matrix particle. The viscogenic agent in the matrix becomes viscous on contact with water and, probably because the viscogenic agent bleeds out onto the surface of the matrix particle, the matrix is rendered adherent to the gastrointestinal mucosa. Therefore, the matrix of the invention is retained in the gastrointestinal tract for a long time during which the active ingredient is gradually dissolved within the gastrointestinal tract and absorbed. Furthermore, the matrix adheres efficiently to a specific site of the gastrointestinal mucosa. Therefore, when the active ingredient is such that its efficacy is dependent on direct exposure, the duration of contact with the desired site of action is prolonged so that the pharmacological activity of the ingredient can be made fully available over a sufficient time. Moreover, even a sparingly water-soluble active ingredient can be released gradually at a selected site within the gastrointestinal tract with the result that its efficacy can be made available over a protracted time period.

In the matrix particle of matrix (A) or of matrix (B), the proportional ratio of the viscogenic agent is generally from 0.005 to 95 percent by weight, preferably, from 0.5 to 30 percent by weight, and, more preferably, from 1 to 10 percent by weight, based on the total weight of the matrix composition.

The matrix (A) composition may be manufactured by dispersing the viscogenic agent, polyglycerol fatty acid ester and active ingredient and the matrix (B) composition may be prepared by dispersing the viscogenic agent, lipid and active ingredient. By way of illustration, the solid matrix comprising the polyglycerol fatty acid ester or lipid and which is solid at ambient temperature is melted by heating it at a temperature above its melting point, then, the viscogenic agent and the active ingredient are added and dispersed therein and the mixture is cooled to yield the matrix composition. The heating temperature for the matrix may, for example, be from 40 to 150°C, preferably, from 50 to 90°C.

When the active ingredient is an acidic drug, the solid base mentioned above may advantageously be added. When it is a basic drug, the enteric polymer mentioned above may be added. When melting the polyglycerol fatty acid ester and/or lipid, the above-mentioned additive may be melted with the ester and/or lipid, or the different materials may be respectively melted and then combined. It is also possible to add the viscogenic agent and additive in particulate form together with the active ingredient.

Fine granules or granules containing the matrix can be manufactured by means of conventional granulating machinery. Such fine granules and granules are preferably prepared under cooling. For example, it is a preferred practice to produce spherical fine granules by spray mist cooling, particularly by spray-chilling. Spray-chilling can be effected by dropping a molten matrix at a constant flow rate onto an high-speed rotating disk driven at 10 to 6000 rpm, preferably 900 to 6,000 rpm, and more preferably 1,000 to 3,000 rpm. The rotary disk for this purpose may be a circular plate disk, smooth circular plate, made of aluminum or like material, which has a diameter of, for example, 5 to 100 cm, preferably 10 to 20 cm. The dropping speed of the molten matrix can be selected according to the desired particle size of fine granules, and is generally from 2 to 200 g/minute, preferably from 5 to 100 g/minute. The resulting granules are closer to true spheres, indicating that a more uniform coating film can be efficiently formed by using the coating composition.

The matrix (A) or (B) can also be prepared by kneading the above-mentioned components with the aid of a solvent and granulating the resultant mass. In this case, the undesirable effect of heat on the active ingredient can be avoided. Therefore, even when the active ingredient is a peptide or a protein, for example, an effective matrix composition can readily be obtained, with the deactivation of the drug being held to a minimum.

The matrix particles of the matrix (C) correspond to particles according to matrix (A) or (B) which have additionally been coated with a coating composition containing at least one viscogenic agent (I) and, in addition to the viscogenic agent(s), at least one member of said polyglycerol fatty acid esters, said enteric polymers and said water-insoluble polymers. In that case, when the viscogenic agent is a substance which is poorly compatible, or is incompatible, with the above-mentioned components, the matrix particle thus coated has a surface film in which said viscogenic agent or agents has or have, been well dispersed. The coating composition may further contain said active ingredient and/or said additives.

The water-insoluble polymer mentioned hereinbefore includes, for example, hydroxypropylmethylcellulose phthalate (J.P. XI), hydroxypropylmethylcellulose acetate succinate (Shin-Etsu Chemical Co., Ltd., Japan), carboxymethylethylcellulose (Freund Industrial Co., Ltd.; CMEC, the Formulary of Non-official Drugs 1986), cellulose acetate trimellitate (Eastman Co., Ltd.), cellulose acetate phthalate (J.P. XI), ethylcellulose (Asahi Chemical Industry Co., Ltd., Japan; FMC), aminoalkyl methacrylate copolymer (Röhm Pharma; Eudragit™ E100, RS, RNIOOL, RSPML, RN100, RSPM), methacrylic acid copolymer L (Röhm Pharma, Eudragit L100), methacrylic acid copolymer L-D (Röhm Pharma, Eudragit L-30-D-55), methacrylic acid copolymer S (Röhm Pharma; Eudragit™ S-100), polyvinyl acetate phthalate (COLORCON™) and Eudragit™ NE30-D (Trade name of Röhm Pharma). These water-insoluble polymers can be used singly or in combination.

The proportion of the viscogenic agent based on the total nonvolatile matter of the coating composition is generally from 0.005 to 100 percent by weight, preferably, from 0.05 to 95 percent by weight, more preferably, from 0.5 to 30 percent by weight, and, in particular, from 1 to 10 percent by weight.

The proportion of the viscogenic agent which is used in combination with at least one of polyglycerol fatty acid esters, enteric polymers and water-insoluble polymers, is from 0.005 to 95 percent by weight, preferably, from 0.5 to 30 percent by weight, and, more preferably, from 1 to 10 percent by weight.

Two or more components selected from among said polyglycerol fatty acid esters, enteric polymers and water-insoluble polymers may be incorporated into the coating composition. When said polyglycerol fatty acid ester(s) is (are) used in combination with another component selected from among said enteric polymers and water-insoluble polymers, the preferred proportion of such other component to each part by weight of the polyglycerol fatty acid ester is from 0.0001 to 1,000 parts by weight, preferably, from 0.01 to 100 parts by weight, and, more preferably, from 0.01 to 10 parts by weight.

The coating amount of the coating composition can be selected according to the type of solid preparation and the desired strength of adhesion to the mucosa. The coating amount relative to the solid preparation is from 0.1 to 30 percent by weight, and, preferably, from 0.5 to 10 percent by weight for tablets, from 0.1 to 50 percent by weight, and, preferably, from 1 to 20 percent by weight, for pills and granules, and from 0.1 to 100 percent by weight, and, preferably, from 1 to 50 percent by weight, for fine granules.

In the coating procedure, the common additives mentioned hereinbefore may be incorporated into the coating composition or may be applied independently of the coating composition, The proportion of such additives to be added may, for example, be from 0.1 to 70 percent by weight, preferably, from 1 to 50 percent by weight, more preferably, from 20 to 50 percent by weight, based on the nonvolatile matter of the coating composition.

Coating can be carried out in conventional manner, such as, e.g., by pan coating, air-suspension or fluidized bed coating or by centrifugal coating. When the coating composition is a solution or dispersion containing water or an organic solvent, the spray-coating method can also be employed. The proportion of such water or organic solvent may, for example, be from 25 to 99 percent by weight. The type of organic solvent is not so critical. Thus, for example, alcohols such as, e.g., methanol, ethanol or isopropyl alcohol; ketones such as, e.g., acetone; and halogenated hydrocarbons such as, e.g., chloroform, dichloromethane or trichloroethane may be employed.

Following the incorporation of the polyglycerol fatty acid ester(s) into the coating composition of the invention, a coated pharmaceutical product can be manufactured by melting the polyglycerol fatty acid ester, with or without the addition of other additives, at an elevated temperature, emulsifying the molten mass with water, spraying the surface of the substrate preparation with the resulting emulsion and drying the coated preparation. An alternative method may comprise preheating the solid substrate preparation with a hot current of air in a coating pan or the like, and feeding the coating composition to the pan so that it may melt and spread over the substrate preparation.

The coating of such a solid preparation is usually carried out at a temperature of 25 to 60°C, and, preferably, 25 to 40°C.

The coating time can be selected according to the coating method, the characteristics and amount of the coating composition and the characteristics of the substrate preparation, among other criteria.

Fine granules, granules, pills, tablets and other dosage forms can be rendered adherent to the mucosa by using the coating composition of the invention. The coating composition can be applied to a broad range of drug substances. For example, it can be applied not only to a matrix particle prepared by melting the polyglycerol fatty acid ester or lipid at an elevated temperature and by adding an active ingredient thereto, but also to a matrix particle containing a physiologically active peptide or protein which is easily deactivated by heat. A matrix particle containing such a thermolabile active ingredient can be manufactured by granulating the active ingredient and said additives, such as a binder, excipient or disintegrator, for example, together with said lipid, where necessary, and without using a polyglycerol fatty acid ester, at a low temperature not causing deactivation of the active ingredient. The matrix particle can also be manufactured by dispersing said components in water or an organic solvent with the use of a kneader, for example, and granulating the kneaded mass.

For all of the matrices (A), (B) and (C), insofar as the viscogenic agent is allowed to exhibit its mucosal adhesivity in the gastrointestinal tract, the matrix may, where necessary, have an enteric or gastric coating, for example. Thus, for example, when the matrix has an enteric coating layer which is adapted to dissolve in the vicinity of the site of absorption, the matrix will adhere to the site of absorption to function as a target-oriented drug delivery system.

The solid preparation according to the present invention may be provided in a variety of dosage forms such as fine granules, granules, pills, tablets obtainable by compression-molding the fine granules or granules, and capsules obtainable by filling capsules with the fine granules or granules. Preferred dosage forms are fine granules and granules. Lipid-containing matrixes (B) and (C) are suitable for fine granules. The particle size distribution of the fine granules may, for example, be 10 to 500 μm for 75 weight % or more of their total weight, more than 500 μm for not more than 5 weight %, and less than 10 μm for not more than 75 weight %. The preferred particle size distribution of the fine granules is 105 to 500 μm for not less than 75 weight %, more than 500 μm for not more than 5 weight %, and not more than 74 μm for not more than 10 weight %. The particle size distribution of the granules may, for example, be 500 to 1410 μm for not less than 90 weight % and not more than 177 μm for not more than 5 weight %.

The following examples and comparative example are merely intended to illustrate the present invention in further detail and should not be construed as defining the scope of the invention.

EXAMPLES

Exmaple 1

Ten grams of stearyl penta(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd. Japan; PS-310) was melted by heating at 85°C. Six grams of idebenone and 2 g of an acrylic acid polymer (The B. F. Goodrich Company; Carbopol 934P) were added to the melt, and the resultant mixture was stirred at 80°C for 15 minutes to give a dispersion. The molten mixture was then dropped onto an aluminum disk (15 cm in diameter) rotating at 1,500 rpm at a rate of 10 g per minute, whereby spherical fine granules passing through a 30-mesh sieve but failing to pass through an 80 mesh sieve (hereinafter referred to briefly as 30/80 mesh) were obtained.

Example 2

The procedure of Example 1 was followed using 11.5 g of stearyl penta(tetra)glyceride, 6.0 g of idebenone and 0.5 g of the same acrylic acid polymer as used in Example 1 to give 30/80 mesh spherical fine granules.

Example 3

The same stearyl penta(tetra)glyceride as used in Example 1 (100 g) was melted by heating at 85°C, 60 g of idebenone was added, and the mixture was stirred for 15 minutes. The molten mixture thus obtained was dropped onto an aluminum disk (15 cm in diameter) rotating at 1,500 rpm at a rate of 10 g per minute, whereby 30/80 mesh spherical fine granules were obtained.

The same acrylic acid polymer as used in Example 1 (4 g) was dispersed in 200 ml of ethanol to give a coating solution.

A centrifugal granulator (Freund Industries, model CF) was charged with 50 g of the above fine granules. Coating was conducted by adding the above coating solution at a rate of 1 ml per minute while a rotating speed of 600 rpm, a hot air temperature of 46°C and a granule temperature of 32°C were maintained. Coated fine granules were thus obtained.

Comparative Example 1

The procedure of Example 3 was followed using 50 g of the same stearyl penta(tetra)glyceride as used in Example 1 and 100 g of idebenone but omitting the acrylic acid polymer coating to give 30/80 mesh spherical fine granules.

Test Example 1

The fine granules obtained in Example 3 and those obtained in Comparative Example 1 were respectively administered orally to rats (weighing 450 g, 12 weeks of age) fasted for 24 hours in a dose of 100 mg/kg together with 0.2 ml of water. Three hours later, the rats were laparotomized and the interior of the stomach was examined. The fine granules obtained in Comparative Example 1 were absent in the stomach whereas the fine granules obtained in Example 3 were found adhering to the stomach wall.

Example 4

The procedure of Example 3 was followed using 100 g of the same stearyl penta(tetra)glyceride as used in Example 1, 80 g of idebenone and 20 g of corn starch to give coated fine granules.

Example 5

The procedure of Example 1 was followed using 12 g of the same stearyl penta(tetra)glyceride, 4 g of stearyl mono(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd., Japan; MS-310), 2 g of riboflavine and 2 g of the same acrylic acid polymer as used in Example 1 to give 30/80 mesh spherical fine granules.

Examples 6 and 7

The procedure of Example 1 was followed using the polyglycerol fatty acid esters specified below, riboflavine and the acrylic acid polymer specified below in the respective amounts (g) shown below to give 30/80 mesh spherical fine granules.

	Example 6	Example 7
Stearyl penta(tetra)glyceride	12.75	13.125
Stearyl mono(tetra)glyceride	4.25	4.375
Riboflavine	2	2
Acrylic acid polymer (same as used in Example 1)	1	0.5

Example 8 to 10

The procedure of example 1 was followed using the polyglycerol fatty acid ester specified below, acetaminophen and the acrylic acid polymer specified below in the respective amounts (g) shown below to give 30/80 mesh spherical fine granules.

	Example 8	Example 9	Example 10
Stearyl penta(tetra) glyceride	13.5	13	12
Acetaminophen	6	6	6
Acrylic acid polymer (same as used in Example 1)	0.5	1	2

Example 11

The procedure of Example 1 was followed using 147.0 g of stearyl penta(tetra)glyceride, 13.4 g of stearyl mono(tetra)glyceride, 15.0 g of vinpocetine and 27.6 g of the same acrylic acid polymer as used in Example 1 to give 30/60 mesh spherical fine granules.

Example 12

The procedure of Example 1 was followed using 79.1 g of stearyl penta(tetra)glyceride, 8.4 g of stearyl mono(tetra)glyceride, 62.0 g of a methacrylic acidmethyl methacrylate copolymer [Röhm Pharama (Germany); Eudragit L100-55] and 7.5 g of vinpocetine to give 30/80 mesh spherical fine granules.

The fine granules obtained were then coated in the same manner as in Example 3 using the same coating solution as used in Example 3 to give coated fine granules.

Example 13

The procedure of Example 1 was followed using 18 g of stearyl penta(tetra)glyceride, 1 g of phenylpropanolamine hydrochloride and 1 g of an acrylic acid polymer (Wako Pure Chemical Industries; HIVISWAKO 104) to give 30/80 mesh spherical fine granules.

Example 14

The procedure of Example 1 was followed using 10 g of stearyl penta(tetra)glyceride, 8 g of AD-5467 and 2 g of the same acrylic acid polymer as used in Example 1 to give 30/80 mesh sperical fine granules.

Comparative Example 2

The procedure of Example 1 was followed using 10 g of stearyl penta(tetra)glyceride and 10 g of AD-5467 to give 30/80 mesh spherical fine granules.

Test Example 2

The fine granules obtained in Example 14 and those obtained in Comparative Example 2 were respectively administered orally to rats in the same manner as in Test Example 1. Three hours later, the rats were laparotomized and the interior of the stomach was examined. The fine granules obtained in Comparative Example 2 were absent in the stomach whereas the fine granules obtained in Example 14 were found adhering to the stomach wall.

Test Example 3

One hundred 30/40 mesh fine granules as sorted from the fine granules obtained in Example 14 and Comparative Example 2 were respectively administered orally to rats (weight 300 to 400 g, 10 to 12 weeks of age) fasted for 24 hours together with 0.5 ml of water At 1, 3, 5 or 8 hours after adminstration, the rats were laparotomized and the fine granules remaining in the stomach and the upper part, middle part, and lower part of the small intestine were respectively counted and the mean values were calculated. The results are shown in Table 1.

Table 1

Time elapsed (hrs)		Stomach	Small intestine		
			Upper	Middle	Lower part
1	Example 14	78.4	9.4	6.1	0
	Comparative Example 2	20.8	4.3	42.8	2.0
3	Example 14	25.3	7.3	22.3	40.5
	Comparative Example 2	2.3	4.6	4.2	62.5
5	Example 14	5.5	2.0	16.0	66.3
	Comparative Example 2	0.3	0	3.0	39.7
8	Example 14	1.0	9.5	15.3	18.9
	Comparative Example 2	0	0	0.4	2.7

Example 15

The procedure of Example 1 was followed using 10 g of hardened cotton seed oil, 8 g of AD-5467 and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh sperical fine granules.

Example 16

The procedure of Example 1 was followed using 16 g of stearic acid, 2 g of riboflavine and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Example 17

The procedure of Example 1 was followed using 27 g of stearyl penta(tetra)glyceride, 3 g of microcrystalline wax (Nippon Seiro Co., Ltd., Japan; Hi-Mic 1080), 2 g of vinpocetine and 8 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Test Example 4

A mixture of 16 g of stearyl penta(tetra)glyceride and 0.5 g of stearyl mono(tetra)glyceride was melted by heating at 85°C. Then, 4 g of a viscogenic agent selected from among the 12 substances mentioned below was added, and the resultant mixture was stirred at 80°C for 15 minutes to effect dispersion.

Acrylic acid polymers: Carbopol 934P, HIVISWAKO 103, HIVISWAKO 104.

Cellulose ethers: HPMC-65SH50, HPMC-65SH4000 (hydroxypropylmethylcellulose 2906), TC-5 (hydroxypropylmethylcellulose 2910), CMC-sodium.

Naturally occurring viscogenic agents: Pectin, tragacanth gum, xanthan gum, gelatin, agar.

The molten mixture was dropped onto an aluminum disk (15 cm in diameter) rotating at 1,500 rm at a rate of 10 g per minute to give 30/42 mesh spherical fine granules.

In a control run, 16 g of stearyl penta(tetra) glyceride and 0.5 g of stearyl mono(tetra)glyceride were melted by heating at 85°C and the molten mixture was dropped onto an aluminum disk (15 cm in diameter) rotating at 1,500 rpm at a rate of 10 g per minute to give 30/42 mesh spherical fine granules.

The fine granules obtained as described above were subjected to in vitro and in vivo tests for investigating the degree of adhesion to the mucosa by the following methods.

In vitro observation

The small intestine of rats (body weights 400 to 500 g, 12 weeks of age) was isolated and washed with several portions of physiological saline. The isolated small intestine was cut to a length of 4 cm and the resulting strip was longitudinally incised. Then, with its mucosal side up, the intestinal strip was mounted on a plastic holder and washed again with several portions of saline. The test fine granules were placed uniformly on the mucosa of the small intestine and the tissues of the small intestine with the granules were placed in a desiccator (93 % RH, room temperature) for 20 minutes. Then, the strip was taken out, washed with saline using a peristaltic pump (flow rate 22 ml/min.) and observed for any adherent fine granules.

The degree of adhesion of fine granules was evaluated according to the following criteria. The results are set forth in Table 2.

Excellent : Very many adherent fine granules
Good : Many adherent fine granules
Fair : Some adherent fine granules
Poor : No adherent fine granules

Table 2

Viscogenic agent	Degree of adhesion
Carbopol 934P	Excellent
HIVISWAKO 103	Excellent
HIVISWAKO 104	Excellent
HPMC-65SH50	Fair
HPMC-65SH4000	Fair
TC-5	Fair
CMC-sodium	Fair
Pectin	Good
Tragacanth gum	Good
Xanthan gum	Fair
Gelatin	Fair
Agar	Good
Control (no viscogenic agent)	Poor

In the in vitro observation, the control fine granules showed no adhesion to the intestinal mucosa. In contrast, the fine granules containing viscogenic agents were found to be adherent to the intestinal mucosa. Particularly excellent adhesion was found for fine granules containing Carbopol 934P, HIVSWAKO 103 and HIVSWAKO 104, respectively.

In vivo observation

Test fine granules were administered orally to rats fasted for 24 hours (body weights 400 to 500 g, 12 weeks of age) in a dose of 100 mg/kg together with 0.5 ml of water. After 3 hours, laparotomy was performed and the gastric mucosa was examined for adhesion of the fine granules. The degree of adhesion was evaluated according to the same criteria as above. The results are set forth in Table 3.

Table 3

Viscogenic agent	Degree of adhesion
Carbopol 934P	Excellent
HIVISWAKO 103	Excellent
HIVISWAKO 104	Excellent
HPMC-65SH50	Good
HPMC-65SH4000	Good
TC-5	Fair
CMC-sodium	Fair
Pectin	Fair
Tragacanth gum	Fair
Xanthan gum	Fair
Gelatin	Fair
Agar	Good
Control (no viscogenic agent)	Poor

In the in vivo observation, the control fine granules were not detected in the stomach but the fine granules containing viscogenic agents were found in the stomach. Particularly the fine granules containing Carbopol 934P, HIVISWAKO 103 and HIVISWAKO 104, respectively, were found adhering in large numbers to the gastric wall.

Example 18

The procedure of Example 1 was followed using 50 g of stearyl penta(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd.; PS-310), 40 g of indomethacin and 10 g of an acrylic acid polymer (Wako Pure Chemical Industries; HIVISWAKO 104) to give 30/80 mesh spherical fine granules.

Test Example 5

The fine granules obtained in Example 18 were orally administered, in the same manner as in Test Example 1, to rats (weighing 300 g, 9 weeks of age) fasted for 24 hours at a dose of 5 mg (as indomethacin) per kg.

In a control group, the same rats as mentioned above were orally given a arabic gum suspension containing 5 % by weight of indomethacin at a dose of 5 mg (as indomethacin) per kg.

The plasma levels (μg/ml) of indomethacin were followed by blood sampling from the rat caudal vein at timed intervals. The results thus obtained are shown below in Table 4.

Table 4

Time (hr)	Blood level (μg/ml)						
	1	2	3	5	8	11	24
Example 18	2.5	6.5	8.9	10.1	9.2	9.2	1.1
Control	17.9	17.5	14.6	11.3	7.5	4.1	0.3

Example 19

The procedure of Example 1 was followed using 101.25 g of stearyl penta(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd.; PS-310), 3.75 g of stearyl mono(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd.; MS-310), 7.5 g of vinpocetine, 15 g of magnesium hydroxide and 22.5 g of an acrylic acid polymer (Wako Pure Chemical Industries; HIVISWAKO 104) to give 30/80 mesh spherical fine granules.

Example 20

The procedure of Comparative Example 2 was followed using 40 g of behenyl hexa(tetra)glyceride (Riken vitamin Co., Ltd.; Poem J-46B) and 10 g of acetaminophen to give 60/100 mesh spherical fine granules.

One part by weight of the fine granules obtained were admixed with 1 part by weight of a molten mixture [stearyl penta(tetra)glyceride (Sakamoto Yakuhin Kogyo Co., Ltd.; PS-310):acrylic acid polymer (Wako Pure Chemical Industries; HIVISWAKO 104):lactose = 16:3:1 (by weight)]. The resultant molten mixture was dropped onto an aluminum disk (15 cm in diameter) rotating at 1,500 rpm at a rate of 10 g per minute, whereby 30/80 mesh spherical fine granules were obtained.

Text Example 6

The fine granules obtained in Example 20 were orally administered to rats in the same manner as in Test Example 1. Three hours later, the rats were laparotomized and the interior of the stomach was examined. The fine granules were found adhering to the stomach wall.

Example 21

The procedure of Example 1 was followed except that 10 g of stearyl penta(tetra)glyceride, 8 g of chlorothiazide and 2 g of the same acrylic acid polymer as used in Example 1 to give 30/80 mesh spherical fine granules.

Comparative Example 3

The procedure of Example 1 was followed except that 10.6 g of stearyl penta(tetra)glyceride, 5.4 g of stearyl mono(tetra)glyceride and 4 g of chlorothiazide to give 30/80 mesh spherical fine granules.

Test Example 7

The fine granules prepared in Example 21 and Comparative Example 3 were respectively administered orally to rats and 3 hours later the animals were laporotomized and observed for the interior of the stomach as in Test Example 1. It was found that whereas the fine granules according to Comparative Example 3 were absent in the stomach, the fine granules of Example 21 remained on the gastric wall.

Test Example 8

The fine granules prepared in Example 21 were orally administered to rats (body weight 250 g, 8 weeks old), deprived of food for 24 hours, in a dose of 10 mg/rat together with 0.2 ml of water.

As a control, a suspension of chlorothiazide in distilled water containing 5 % (w/v) of arabic gum was orally administered in a dose of 10 mg (as chlorothiazide)/rat.

The blood was serially taken from the causal vein of the rat to investigate a time course of plasma chlorothiazide concentration (μg/ml). The results are set forth in Table 5.

Table 5

Time (hr)	Blood level (μg/ml)						
	0.5	1	2	3	5	8	10
Example 21	0.39	0.37	0.38	0.52	1.17	0.93	0.78
Control	0.63	0.50	0.71	0.58	0.42	0.34	0.21

The rats treated with the fine granules of Example 21 showed a higher plasma concentration of chlorothiazide over a longer time period.

Example 22

The procedure of Example 1 was followed except that 12 g of stearyl penta(tetra)glyceride, 6 g of buprenorphine hydrochloride and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Example 23

The procedure of Example 1 was followed except that 9.5 g of stearyl penta(tetra)glyceride, 0.5 g of stearyl mono(tetra)glyceride, 2 g of sucralfate (Nippon Synthetic Chemical Industry, Japan; Sulcose) and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Example 24

The procedure of Example 1 was followed except that 13.5 g of behenyl hexa(tetra)glyceride (Riken Vitamin Co., Ltd.; Poem J-46B), 0.5 g of stearyl mono(tetra)glyceride, 1 g of dihydrocodeine phosphate, 2 g of magnesium hydroxide and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Example 25

The procedure of Example 1 was followed except that 13.5 g of behenyl hexa(tetra)glyceride, 0.5 g of stearyl mono(tetra)glyceride, 1 g of dihydrocodeine phosphate, 3 g of calcium carbonate and 2 g of the same acrylic acid polymer as used in Example 13 to give 30/80 mesh spherical fine granules.

Example 26

The fine granules (25 g) obtained in Example 5 were coated in the following manner to give coated fine granules. Thus, a miniature CF equipment (CF Granulator, Freund Industries) was charged with 25 g of fine granules and with the rotor speed set at 550 rpm, a 5 % (w/v) solution of Eudragit L100-55 (Trade name of Röhm Pharma) in ethanol was sprayed at a rate of 0.7 ml/minute to give 24/80 mesh sperical fine granules.

Example 27

The procedure of Example 26 was followed except that 25 g of the fine granules obtained in Example 5 were spray-coated with a 5 % (w/v) solution of hydroxypropylcellulose (Nippon Soda Co., Ltd., Japan; HPC-L) in ethanol to give 24/80 mesh spherical fine granules.

Example 28

The procedure of Example 1 was followed except that 10 g of stearyl penta(tetra)glyceride, 4 g of chlorothiazide and 2 g of NOVEON AA1 (Trade name of The B. F. Goodrich Company) to give 30/80 mesh spherical fine granules.

Example 29

Fifty grams of the fine granules obtained in Example 5 were mixed with 45 g of crystalline cellulose, 5 g of croscarmellose sodium (Ac-Di-Sol; Trade name of FMC Corporation) and 0.3 g of magnesium stearate and the mixture was compression-molded with a punch having a flat surface, 100 mm in diameter, at 0.5 ton/cm^2 to give tablets.

Example 30

The procedure of Example 1 was followed except that 15 g of behenyl hexa(tetra)glyceride, 2 g of AG 1789 and 3 g of the acrylic acid polymer used in Example 13 to give 30/80 mesh spherical fine granules.

Test Example 9

The fine granules obtained in Example 30 was orally administered to rats and 3 hours later the animals were laparotomized and observed for the interior of the stomach as in Example 1. The fine granules were found adhering to the gastric wall.

Example 31

To 500 g of stearyl penta(tetra)glyceride was added 500 g of stearyl mono(tetra)glyceride and the mixture was melted by heating at 90°C and dropped on an aluminum disk, 15 cm in diameter, revolving at 2,000 rpm at the rate of 20 g/minute to give 42/60 mesh spherical polyglycerol fatty acid ester granules.

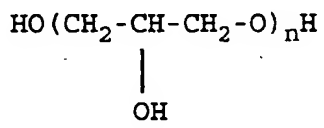
A fluidized-bed granulator (Fuji Sangyo Co., Ltd., Japan; FD-3S) was charged with 100 g of the 42/60 mesh polyglycerol fatty acid ester, 50 g of the same acrylic acid polymer as used in Example 13 and 40 g of riboflavine and the charge was fluidized at an air temperature of 54°C. When it was confirmed that the floating acrylic acid polymer and riboflavin particles were no longer observed in the fluidized bed, the heat source was switched off. On cooling, there were obtained granules.

Claims

1. A gastrointestinal mucosa-adherent matrix which is solid at ambient temperature, and which comprises (i) an active ingredient; (ii) a polyglycerol fatty acid ester and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (iii) a viscogenic agent having the property of becoming viscous on contact with water and selected from (a) acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers, in which matrix said viscogenic agent is dispersed at least in the neighbourhood of the surface layer of each matrix particle, and, optionally, said matrix particle additionally has a coating layer formed from a coating composition containing said viscogenic agent.

2. A gastrointestinal mucosa-adherent matrix according to claim 1, wherein the content of said viscogenic agent is from 0.005 to 95 percent by weight based on the total weight of said matrix particle.

3. A gastrointestinal mucosa-adherent matrix according to claim 1 or claim 2, wherein said polygylcerol fatty acid ester is an ester of a polyglycerol of the formula (I):



(I)

wherein n represents the degree of polymerization which is an integer of not less than 2, with a saturated or unsaturated higher fatty acid.

4. A gastrointestinal mucosa-adherent matrix according to claim 3, wherein n is in the range of from 2 to 50.

5. A gastrointestinal mucosa-adherent matrix according to claim 3 or claim 4, wherein said fatty acid is a saturated or unsaturated higher fatty acid containing from 8 to 40 carbon atoms.

6. A gastrointestinal mucosa-adherent matrix according to any of claims I to 5, wherein said polyglycerol fatty acid ester is selected from behenyl hexa-(tetra)glyceride, stearyl penta(tetra)glyceride, stearyl mono(tetra)glyceride, stearyl penta(hexa)glyceride, stearyl sesqui(hexa)glyceride, stearyl mono(deca)glyceride and mixtures thereof.

7. A gastrointestinal mucosa-adherent matrix according to any of claims I to 6, wherein said polyglycerol fatty acid ester has an HLB (hydrophile-lipophile balance) value of from 1 to 22.

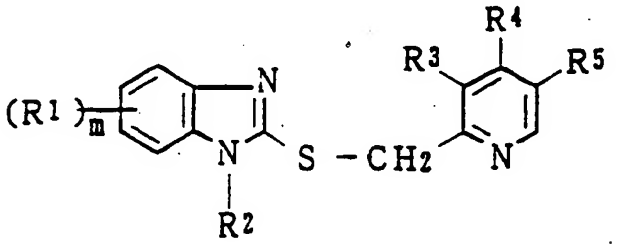
8. A gastrointestinal mucosa-adherent matrix according to any of claims I to 7, wherein said polyglycerol fatty acid ester has a melting point of from 15 to 80°C.

9. A gastrointestinal mucosa-adherent matrix according to any of claims I to 7, wherein said lipid has a melting point

of from 40 to 120°C.

10. A gastrointestinal mucosa-adherent matrix according to any of claims I to 9, wherein said active ingredient (i) is an antiulcer agent or a therapeutic drug for gastritis.

11. A gastrointestinal mucosa-adherent matrix according to any of claims I to 10, wherein said active ingredient (i) is a compound of the following formula (II) or a physiologically acceptable salt thereof:



(II)

wherein R^1 represents hydrogen, alkyl, halogen, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsufinyl; R^2 represents hydrogen, alkyl, acyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl; R^3 and R^5 may be the same or different, and each represents hydrogen, alkyl, alkoxy or alkoxyalkoxy; R^4 represents hydrogen, alkyl, alkoxy, which may be fluorinated, alkoxyalkoxy, alkenyloxy, which may be fluorinated, or alkynyloxy, which may be fluorinated, and m represents 0 to an integer of 1 to 4.

12. A gastrointestinal mucosa-adherent matrix according to claim II, wherein, in said compound of the formula (II), R^1, R^2 and R^5 are each hydrogen and R^3 is hydrogen or methyl.

13. A gastrointestinal mucosa-adherent matrix according to claim 11 or claim 12, wherein, in said compound of the formula (II), R^4 is a fluorinated C_{1-4} alkoxy group.

14. A gastrointestinal mucosa-adherent matrix according to claim 11, wherein, in said compound of the formula (II), R^1 is hydrogen, fluorine, methoxy or trifluoromethyl as substituted in the 5-position; R^2 is hydrogen; R^3 is hydrogen or methyl; R^4 is a C_{1-4} alkoxy, which may be fluorinated, 2-propenyloxy or allyl; R^5 is hydrogen or methyl, and m=1.

15. A gastrointestinal mucosa-adherent matrix according to any of claims I to 14, which comprises a water-insoluble or sparingly water-soluble solid base together with an acidic active ingredient.

16. A gastrointestinal mucosa-adherent matrix according to any of claims I to 14, which comprises an enteric polymer together with a basic active ingredient.

17. A gastrointestinal mucosa-adherent matrix according to any of claims I to 16, wherein the content of said polyglycerol fatty acid ester and/or said lipid in said matrix particle is from 0.001 to 10,000 parts by weight relative to one part by weight of said active ingredient.

18. A gastrointestinal mucosa-adherent matrix according to Claim 3, wherein the matrix comprises, as component (ii) an ester of a polyglycerol of formula (I), wherein n is 2 to 50, with a saturated or unsaturated higher fatty acid of 8 to 40 carbon atoms, the content of said polyglycerol fatty acid ester being from 0.001 to 10,000 parts by weight relative to one part by weight of said active ingredient (i).

19. A gastrointestinal mucosa-adherent matrix according to claim I, wherein said matrix has a melting point in the range of from 30 to 120°C., inclusive.

20. A solid pharmaceutical preparation comprising a gastrointestinal mucosa-adherent matrix according to any of claims I to 19.

21. A matrix coating composition for rendering matrix-based dosage forms of a solid pharmaceutical composition

adherent to the gastrointestinal mucosa, which coating composition comprises (A) at least one polyglycerol fatty acid ester (PGEF) and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (B) at least one viscogenic agent having the property of becoming viscous on contact with water and selected from acrylic acid polymers having a molecular weight in the range of from l,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers.

22. A coating composition according to claim 21, which, on a non-volatile matter basis, contains from 0.005 to 100 percent by weight of said viscogenic agent (B).

23. The use of a coating composition according to claim 21 or claim 22 to coat the particles of a gastrointestinal mucosa-adherent matrix according to any of claims l to 20.

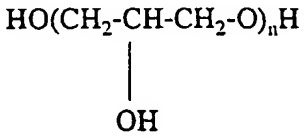
24. A method for manufacturing a gastrointestinal mucosa-adherent matrix which is solid at ambient temperature, and which comprises (i) an active ingredient; (ii) a polyglycerol fatty acid ester and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (iii) a viscogenic agent having the property of becoming viscous on contact with water and selected from (a) acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers, in which matrix said viscogenic agent is dispersed at least in the neighbourhood of the surface layer of each matrix particle, and, optionally, said matrix particle additionally has a coating layer formed from a coating composition containing said viscogenic agent, which method comprises;

(A) dispersing (i) said active ingredient and (iii) said viscogenic agent in (ii) said polyglycerol fatty acid ester and/or the lipid, or (B) kneading the components (i), (ii) and (iii), and

granulating the resulting mass,
optionally followed by coating the resulting granule with the coating composition containing said viscogenic agent.

25. A method according to claim 24, wherein the content of said viscogenic agent is from 0.005 to 95 percent by weight based on the total weight of said matrix particle.

26. A method according to claim 24 or 25, wherein said polyglycerol fatty acid ester is an ester of a polyglycerol of the formula (I):



(I)

wherein n represents the degree of polymerisation which is an integer of not less than 2,
with a saturated or unsaturated higher fatty acid.

27. A method according to claim 26, wherein n is in the range of from 2 to 50.

28. A method according to claim 26 or 27, wherein said fatty acid is a saturated or unsaturated higher fatty acid containing from 8 to 40 carbon atoms.

29. A method according to any of claims 24 to 28, wherein said polyglycerol fatty acid ester is selected from behenyl hexa-(tetra)glyceride, stearyl penta(tetra)glyceride, stearyl mono(tetra)glyceride, stearyl penta(hexa)glyceride, stearyl sesqui(hexa)glyceride, stearyl mono(deca)glyceride and mixtures thereof.

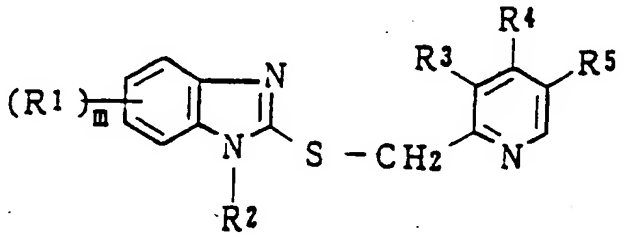
30. A method according to any of claims 24 to 29, wherein said polyglycerol fatty acid ester has an HLB (hydrophile-lipophile balance) value of from 1 to 22.

31. A method according to any of claims 24 to 30, wherein said polyglycerol fatty acid ester has a melting point of from 15 to 80°C.

32. A method according to any of claims 24 to 30, wherein said lipid has a melting point of from 40 to 120°C.

33. A method according to any of claims 24 to 32, wherein said active ingredient (i) is an antiulcer agent or a therapeutic drug for gastritis.

34. A method according to any of claims 24 to 33, wherein said active ingredient (i) is a compound of the following formula (II) or a physiologically acceptable salt thereof:



(II)

wherein R^1 represents hydrogen, alkyl, halogen, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, carbamoyl, carbamoyalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl; R^2 represents hydrogen, alkyl, acyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl; R^3 and R^5 may be the same or differnet, and each represents hydrogen, alkyl, alkoxy or alkoxyalkoxy; R^4 represents hydrogen, alkyl, alkoxy, which may be fluorinated, alkoxyalkoxy, alkenyloxy, which may be fluorinated, or alkynyloxy, which may be fluorinated and m represents 0 to an integer of 1 to 4.

35. A method according to claim 34, wherein, in said compound of the formula (II), R^1, R^2 and R^5 are each hydrogen and R^3 is hydrogen or methyl.

36. A method according to claim 34 or 35, wherein, in said compound of the formula (II), R^4 is a fluorinated C_{1-4} alkoxy group.

37. A method according to claim 34, wherein, in said compound of the formula (II), R^1 is hydrogen, fluorine, methoxy or trifluoromethyl as substituted in the 5-position; R^2 is hydrogen; R^3 is hydrogen or methyl; R^4 is a C_{1-4} alkoxy, which may be fluorinated, 2-propenyloxy or allyl; R^5 is hydrogen or methyl, and m=1.

38. A method according to any of claims 24 to 37, in which the matrix comprises a water-insoluble or sparingly water-soluble solid base together with an acidic active ingredient.

39. A method according to any of claims 24 to 37, in which the matrix comprises an enteric polymer together with a basic active ingredient.

40. A method according to any of claims 24 to 39, wherein the content of said polyglycerol fatty acid ester and/or said lipid in said matrix particle is from 0.001 to 10,000 parts by weight relative to one part by weight of said active ingredient.

41. A method according to claim 26, wherein the matrix comprises, as component (ii) an ester of a polyglycerol of formula (I), wherein n is 2 to 50, with a saturated or unsaturated higher fatty acid of 8 to 40 carbon atoms, the content of said polyglycerol fatty acid ester being from 0.001 to 10,000 parts by weight relative to one part by weight of said active ingredient (i).

42. A method according to claim 24, wherein said matrix has a melting point in the range of from 30 to 120°C., inclusive.

43. A method for manufacturing a solid pharmaceutical preparation comprising a gastrointestinal mucosa-adherent matrix which is solid at ambient temperature, and which comprises (i) an active ingredient; (ii) a polyglycerol fatty acid ester and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (iii) a viscogenic agent having the property of becoming viscous on contact with water and selected from (a) acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers, in which matrix said viscogenic agent is dispersed at least in

the neighbourhood of the surface layer of each matrix particle, and, optionally, said matrix particle additionally has a coating layer formed from a coating composition containing said viscogenic agent,

which method comprises granulating said matrix to obtain fine granules or granules, optionally followed by compression-molding the fine granules or granules to obtain tablets or by filling capsules with the fine granules or granules to obtain capsules.

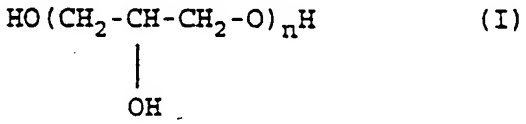
44. A method for manufacturing a matrix-based dosage form of a solid pharmaceutical composition adherent to the gastrointestinal mucosa, which method comprises coating a matrix particle containing an active ingredient with a coating composition comprising (A) at least one polyglycerol fatty acid ester (PGEF) and/or a lipid selected from C_{14-22} saturated fatty acids and salts thereof; and (B) at least one viscogenic agent having the property of becoming viscous on contact with water and selected from acrylic acid polymers having a molecular weight in the range of from 1,000,000 to 5,000,000, and containing 58.0 to 63.0 percent by weight of carboxyl groups, and salts of said acrylic acid polymers.

Patentansprüche

1. An der Magen-Darm-Schleimhaut haftende Matrix, die bei Umgebungstemperatur fest ist und die (i) einen Wirkstoff; (ii) einen Polyglycerinfettsäureester und/oder ein Lipid, ausgewählt aus gesättigten C_{14-22}-Fettsäuren und Salzen davon; und (iii) ein viskogenes Mittel umfaßt, das die Eigenschaft aufweist, bei Berührung mit Wasser viskos zu werden, und das aus (a) Acrylsäurepolymeren mit einem Molekulargewicht im Bereich von 1.000.000 bis 5.000.000, die 58,0 bis 63,0 Gew.-% Carboxylgruppen enthalten, und aus Salzen der Acrylsäurepolymere ausgewählt ist, in welcher Matrix das viskogene Mittel zumindest in der Nachbarschaft der Oberflächenschicht eines jeden Matrixteilchens dispergiert ist, und das Matrixteilchen gegebenenfalls zusätzlich eine Überzugsschicht aufweist, die aus einer das viskogene Mittel enthaltenden Überzugszusammensetzung gebildet ist.

2. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 1, worin der Gehalt an viskogenem Mittel, bezogen auf das Gesamtgewicht des Matrixteilchens, 0,005 bis 95 Gew.-% beträgt.

3. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 1 oder 2, worin der Polyglycerinfettsäureester ein Ester eines Polyglycerins der Formel (I):



(I)

worin n den Polymerisationsgrad darstellt, der eine ganze Zahl nicht unter 2 ist, mit einer gesättigten oder ungesättigten höheren Fettsäure ist.

4. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 3, worin n im Bereich von 2 bis 50 liegt.

5. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 3 oder 4, worin die Fettsäure eine gesättigte oder ungesättigte höhere Fettsäure ist, die 8 bis 40 Kohlenstoffatome enthält.

6. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 5, worin der Polyglycerinfettsäureester aus Behenylhexa(tetra)glycerid, Stearylpenta(tetra) glycerid, Stearylmono(tetra)glycerid, Stearylpenta(hexa)glycerid, Stearylsesqui(hexa)glycerid, Stearylmono(deca)glycerid und Gemischen daraus ausgewählt ist.

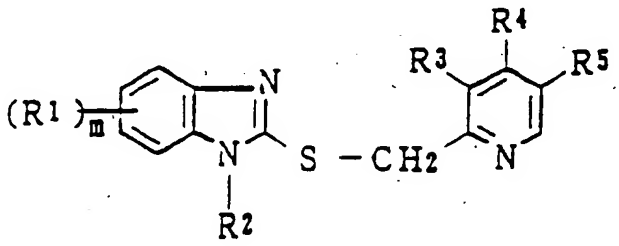
7. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 6, worin der Polyglycerinfettsäureester einen HLB (Hydrophil-Lipophil-Gleichgewicht)-Wert von 1 bis 22 aufweist.

8. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 7, worin der Polyglycerinfettsäureester einen Schmelzpunkt von 15 bis 80°C aufweist.

9. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 7, worin das Lipid einen Schmelzpunkt von 40 bis 120°C aufweist.

10. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 9, worin der Wirkstoff (i) ein geschwürhemmendes Mittel oder ein Arzneimittel zur Gastritistherapie ist.

11. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 10, worin der Wirkstoff (i) eine Verbindung der folgenden Formel (II) oder ein physiologisch akzeptables Salz davon ist:



(II)

worin R^1 für Wasserstoff, Alkyl, Halogen, Cyano, Carboxy, Alkoxycarbonyl, Alkoxycarbonylalkyl, Carbamoyl, Carbamoylalkyl, Hydroxy, Alkoxy, Hydroxalkyl, Trifluormethyl, Acyl, Carbamoyloxy, Nitro, Acyloxy, Aryl, Aryloxy, Alkylthio oder Alkylsulfinyl steht; R^2 für Wasserstoff, Alkyl, Acryl, Alkoxycarbonyl, Carbamoyl, Alkylcarbamoyl, Dialkylcarbamoyl, Alkylcarbonylmethyl, Alkoxycarbonylmethyl oder Alkylsulfonyl steht; R^3 und R^5 gleich oder voneinander verschieden sein können und jeweils für Wasserstoff, Alkyl, Alkoxy oder Alkoxyalkoxy stehen; R^4 für Wasserstoff, Alkyl, Alkoxy, das fluoriert sein kann, Alkoxyalkoxy, Alkenyloxy, das fluoriert sein kann, oder Alkinyloxy, das fluoriert sein kann, steht, und m für 0 bis zu einer ganzen Zahl von 1 bis 4 steht.

12. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 11, worin die Verbindung mit der Formel (II), R^1, R^2 und R^5 jeweils Wasserstoff sind und R^3 Wasserstoff oder Methyl ist.

13. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 11 oder 12, worin in der Verbindung mit der Formel (II) R^4 eine fluorierte C_{1-4}-Alkoxygruppe ist.

14. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 11, worin in der Verbindung mit der Formel (II) R^1 Wasserstoff, Fluor, Methoxy oder Trifluormethyl als Substituent in Position 5 ist; R^2 Wasserstoff ist; R^3 Wasserstoff oder Methyl ist; R^4 ein C_{1-4}-Alkoxy, das fluoriert sein kann, 2-Propenyloxy oder Allyl ist; R^5 Wasserstoff oder Methyl ist und m = 1.

15. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 14, die eine wasserunlösliche oder schwach wasserlösliche feste Basis gemeinsam mit einem sauren Wirkstoff umfaßt.

16. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 14, die ein Darm-Polymer gemeinsam mit einem basischen Wirkstoff umfaßt.

17. An der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 16, worin der Gehalt des Polyglycerinfettsäureesters und/oder des Lipids im Matrixteilchen von 0,001 bis 10.000 Gewichtsteile, bezogen auf 1 Gewichtsteil Wirkstoff, beträgt.

18. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 3, worin die Matrix als Komponente (ii) einen Ester eines Polyglycerins der Formel (I), worin n 2 bis 50 ist, mit einer gesättigten oder ungesättigten höheren Fettsäure mit 8 bis 40 Kohlenstoffatomen umfaßt, wobei der Gehalt an Polyglycerinfettsäureester von 0,001 bis 10.000 Gewichtsteile bezogen auf 1 Gewichtsteil Wirkstoff (i) beträgt.

19. An der Magen-Darm-Schleimhaut haftende Matrix nach Anspruch 1, worin die Matrix einen Schmelzpunkt im Bereich von 30 bis einschließlich 120°C aufweist.

20. Festes pharmazeutisches Präparat, das eine an der Magen-Darm-Schleimhaut haftende Matrix nach einem der Ansprüche 1 bis 19 umfaßt.

21. Matrixüberzugszusammensetzung, um Dosierformen auf Matrixbasis einer festen pharmazeutischen Zusammensetzung an der Magen-Darm-Schleimhaft haftend zu machen, welche Überzugszusammensetzung (A) zumindest einen Polyglycerinfettsäureester (PGEF) und/oder ein Lipid, ausgewählt aus C_{14-22}-Fettsäuren und Salzen davon,

und (B) zumindest ein viskogenes Mittel umfaßt, das die Eigenschaft aufweist, beim Kontakt mit Wasser viskos zu werden, und das aus Acrylsäurepolymeren mit einem Molekulargewicht im Bereich von 1.000.000 bis 5.000.000, die 58,0 bis 63,0 Gew.-% Carboxylgruppen enthalten, und aus Salzen dieser Acrylsäurepolymeren ausgewählt ist.

22. Überzugszusammensetzung nach Anspruch 21, die bezogen auf nicht-flüchtige Bestandteile 0,005 bis 100 Gew.-% des viskogenen Mittels (B) umfaßt.

23. Verwendung einer Überzugszusammensetzung nach Anspruch 21 oder 22 zum Beschichten der Teilchen einer an der Magen-Darm-Schleimhaut haftenden Matrix nach einem der Ansprüche 1 bis 20.

24. Verfahren zur Herstellung einer an der Magen-Darm-Schleimhaut haftenden Matrix, die bei Umgebungstemperatur fest ist, und die (i) einen Wirkstoff; (ii) einen Polyglycerinfettsäureester und/oder ein Lipid, ausgewählt aus gesättigten C_{14-22}-Fettsäuren und Salzen davon; und (iii) ein viskogenes Mittel umfaßt, das die Eigenschaft aufweist, bei Berührung mit Wasser viskos zu werden, und das aus (a) Acrylsäurepolymeren mit einem Molekulargewicht im Bereich von 1.000.000 bis 5.000.000, die 58,0 bis 63,0 Gew.-% Carboxylgruppen enthalten, und aus Salzen dieser Acrylsäurepolymeren ausgewählt ist, in welcher Matrix das viskogene Mittel zumindest in der Nachbarschaft der Oberflächenschicht eines jeden Matrixteilchens dispergiert ist, und das Matrixteilchen gegebenenfalls zusätzlich eine Überzugsschicht aufweist, die aus einer das viskogene Mittel enthaltenden Überzugszusammensetzung gebildet ist, welches Verfahren umfaßt:

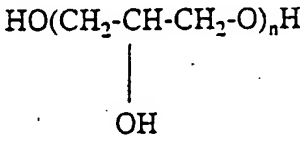
(A) das Dispergieren (i) des Wirkstoffs und (iii) des viskogenen Mittels in (ii) dem Polyglycerinfettsäureester und/oder dem Lipid, oder (B) das Kneten der Komponenten (i), (ii) und (iii), und

das Granulieren der resultierenden Masse,

gegebenenfalls gefolgt vom Beschichten des resultierenden Granulats mit der das viskogene Mittel enthaltenden Überzugszusammensetzung.

25. Verfahren nach Anspruch 24, worin der Gehalt an viskogenem Mittel, bezogen auf das Gesamtgewicht des Matrixteilchens, von 0,005 bis 95 Gew.-% beträgt.

26. Verfahren nach Anspruch 24 oder 25, worin der Polyglycerinfettsäureester ein Ester eines Polyglycerins mit der Formel (I):



(I)

worin n den Polymerisationsgrad darstellt, der eine ganze Zahl nicht unter 2 ist,
mit einer gesättigten oder ungesättigten höheren Fettsäure ist.

27. Verfahren nach Anspruch 26, worin n im Bereich von 2 bis 50 liegt.

28. Verfahren nach Anspruch 26 oder 27, worin die Fettsäure eine gesättigte oder ungesattigte höhere Fettsäure ist, die von 8 bis 40 Kohlenstoffatome enthält.

29. Verfahren nach einem der Ansprüche 24 bis 28, worin der Polyglycerinfettsäureester aus Behenylhexa(tetra)glycerid, Stearylpenta(tetra)glycerid, Stearylmono(tetra)glycerid, Stearylpenta(hexa)glycerid, Stearylsesqui(hexa)glycerid, Stearylmono(deca)glycerid und Gemischen daraus ausgewählt ist.

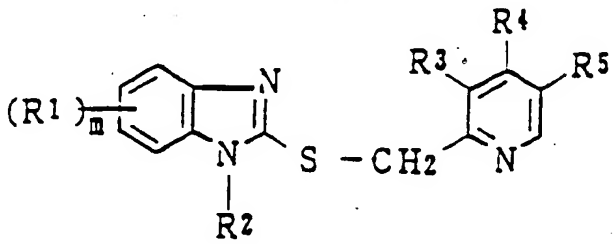
30. Verfahren nach einem der Ansprüche 24 bis 29, worin der Polyglycerinfettsäureester einen HLB (Hydrophil-Lipophil-Gleichgewicht)-Wert von 1 bis 22 aufweist.

31. Verfahren nach einem der Ansprüche 24 bis 30, worin der Polyglycerinfettsäureester einen Schmelzpunkt von 15 bis 80°C aufweist.

32. Verfahren nach einem der Ansprüche 24 bis 30, worin das Lipid einen Schmelzpunkt von 40 bis 120°C aufweist.

33. Verfahren nach einem der Ansprüche 24 bis 32, worin der Wirkstoff (i) ein geschwürhemmendes Mittel oder ein Arzneimittel zur Gastritistherapie ist.

34. Verfahren nach einem der Ansprüche 24 bis 33, worin der Wirkstoff (i) eine Verbindung der folgenden Formel (II) oder ein physiologisch akzeptables Salz davon ist:



(II)

worin R^1 für Wasserstoff, Alkyl, Halogen, Cyano, Carboxy, Alkoxycarbonyl, Alkoxycarbonylalkyl, Carbamoyl, Carbamoyalkyl, Hydroxy, Alkoxy, Hydroxalkyl, Trifluormethyl, Acyl, Carbamoyloxy, Nitro, Acyloxy, Aryl, Aryloxy, Alkylthio oder Alkylsulfinyl steht; R^2 für Wasserstoff, Alkyl, Acryl, Alkoxycarbonyl, Carbamoyl, Alkylcarbamoyl, Dialkylcarbamoyl, Alkylcarbonylmethyl, Alkoxycarbonylmethyl oder Alkylsulfonyl steht; R^3 und R^5 gleich oder voneinander verschieden sein können und jeweils für Wasserstoff, Alkyl, Alkoxy oder Alkoxyalkoxy stehen; R^4 für Wasserstoff, Alkyl, Alkoxy, das fluoriert sein kann, Alkoxyalkoxy, Alkenyloxy, das fluoriert sein kann, oder Alkinyloxy, das fluoriert sein kann, steht, und m für 0 bis zu einer ganzen Zahl von 1 bis 4 steht.

35. Verfahren nach Anspruch 34 worin in der Verbindung mit der Formel (II), R^1, R^2 und R^5 jeweils Wasserstoff sind und R^3 Wasserstoff oder Methyl ist.

36. Verfahren nach Anspruch 34 oder 35, worin in der Verbindung mit der Formel (II) R^4 eine fluorierte C_{1-4}-Alkoxygruppe ist.

37. Verfahren nach Anspruch 34, worin in der Verbindung mit der Formel (II) R^1 Wasserstoff, Fluor, Methoxy oder Trifluormethyl als Substituent in Position 5 ist; R^2 Wasserstoff ist; R^3 Wasserstoff oder Methyl ist; R^4 ein C_{1-4}-Alkoxy, das fluoriert sein kann, 2-Propenyloxy oder Allyl ist; R^5 Wasserstoff oder Methyl ist und m = 1.

38. Verfahren nach einem der Ansprüche 24 bis 37, bei dem die Matrix eine wasserunlösliche oder gering wasserlösliche feste Basis gemeinsam mit einem sauren Wirkstoff umfaßt.

39. Verfahren nach einem der Ansprüche 24 bis 37, bei dem die Matrix ein Darm-Polymer gemeinsam mit einem basischen Wirkstoff umfaßt.

40. Verfahren nach einem der Ansprüche 24 bis 39, worin der Gehalt des Polyglycerinfettsäureester und/oder des Lipids im Matrixteilchen von 0,001 bis 10.000 Gewichtsteile, bezogen auf 1 Gewichtsteil Wirkstoff, beträgt.

41. Verfahren nach Anspruch 26, worin die Matrix als Komponente (ii) einen Ester eines Polyglycerins der Formel (I), worin n 2 bis 50 ist, mit einer gesättigten oder ungesättigten höheren Fettsäure mit 8 bis 40 Kohlenstoffatomen umfaßt, wobei der Gehalt des Polyglycerinfettsäureesters von 0,001 bis 10.000 Gewichtsteile, bezogen auf 1 Gewichtsteil Wirkstoff (i), beträgt.

42. Verfahren nach Anspruch 24, worin die Matrix einen Schmelzpunkt im Bereich von 30 bis einschließlich 120°C aufweist.

43. Verfahren zur Herstellung eines festen pharmazeutischen Präparats, das eine an der Magen-Darm-Schleimhaut haftende Matrix umfaßt, die bei Umgebungstemperatur fest ist, und die (i) einen Wirkstoff; (ii) einen Polyglycerinfettsäureester und/oder ein Lipid, ausgewählt aus gesättigten C_{14-22}-Fettsäuren und Salzen davon; und (iii) ein viskogenes Mittel umfaßt, das die Eigenschaft aufweist, bei Kontakt mit Wasser viskos zu werden, und das aus (a) Acrylsäurepolymeren mit einem Molekulargewicht im Bereich von 1.000.000 bis 5.000.000, die 58,0 bis 63,0 Gew.-% Carboxylgruppen enthalten, und aus Salzen dieser Acrylsäurepolymeren ausgewählt ist, in welcher Matrix das

viskogene Mittel zumindest in der Nachbarschaft der Oberflächenschicht eines jeden Matrixteilchens dispergiert ist, und das Matrixteilchen gegebenenfalls zusätzlich eine Überzugsschicht aufweist, die aus einer das viskogene Mittel enthaltenden Überzugszusammensetzung gebildet ist,
welches Verfahren das Granulieren der Matrix umfaßt, um feines Granulat oder Granulat zu erhalten, gegebenenfalls gefolgt vom Druckformen des feinen Granulats oder Granulats, um Tabletten zu erhalten, oder vom Füllen von Kapseln mit feinem Granulat oder Granulat, um Kapseln zu erhalten.

44. Verfahren zur Herstellung einer Dosierform auf Matrixbasis einer festen pharmazeutischen Zusammensetzung, die an der Magen-Darm-Schleimhaut anhaftet, welches Verfahren das Beschichten eines Matrixteilchens, das einen Wirkstoff enthält, mit einer Beschichtungszusammensetzung umfaßt, die (A) zumindest einen Polyglycerinfettsäureester (PGEF) und/oder ein Lipid, ausgewählt aus gesättigten C_{14-22}-Fettsäuren und Salzen davon; und (B) ein viskogenes Mittel, das die Eigenschaft aufweist, bei Kontakt mit Wasser viskos zu werden, und das aus Acrylsäurepolymeren mit einem Molekulargewicht im Bereich von 1.000.000 bis 5.000.000, die 58,0 bis 63,0 Gew.-% Carboxylgruppen enthalten, und aus Salzen dieser Acrylsäurepolymeren ausgewählt ist, umfaßt.

Revendications

1. Matrice adhérant à la muqueuse gastro-intestinale, qui est solide à la température ordinaire et qui comprend (i) une substance active; (ii) un ester d'acide gras de polyglycérol et/ou un lipide choisi parmi les acides gras saturés en C_{14-22} et leurs sels; et (iii) un agent de viscosité ayant la propriété de devenir visqueux au contact de l'eau et choisi parmi (a) les polymères d'acide acrylique ayant un poids moléculaire dans le domaine de 1 000 000 à 5 000 000 et contenant de 58,0 à 63,0 pour-cent en poids de groupes carboxyliques, et les sels desdits polymères d'acide acrylique, ledit agent de viscosité étant dispersé dans cette matrice au moins au voisinage de la couche superficielle de chacune des particules de la matrice et, cas échéant, lesdites particules de la matrice comportent en outre une couche de revêtement formée à partir d une composition de revêtement contenant ledit agent de viscosité.

2. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 1, dans laquelle la teneur en ledit agent de viscosité est de 0,005 à 95% en poids. par rapport au poids total desdites particules de la matrice.

3. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 1 ou la revendication 2, dans laquelle ledit ester d'acide gras de polyglycérol est un ester d'un polyglycérol de formule (I):

$$HO\left(CH_2\text{-}\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_2\text{-}O\right)_n H \qquad (I)$$

dans laquelle n représente le degré de polymérisation, qui est un nombre entier non inférieur à 2, et d'un acide gras supérieur, saturé ou insature.

4. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 3, dans laquelle n se situe dans le domainde de 2 à 50.

5. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 3 ou la revendication 4, dans laquelle ledit acide gras est un acide gras supérieur, saturé ou insaturé, comportant de 8 à 40 atomes de carbone.

6. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 5, dans laquelle ledit ester d'acide gras de polyglycérol est choisi parmi l'hexa(tétra)glycéride de béhényle, le penta(tétra)glycéride de stéaryle, le mono(tétra)glycéride de stéaryle, le penta(hexa)glycéride de stéaryle, le sesqui(hexa)glycéride de stéaryle, le mono(déca)glycéride de stéaryle et les mélanges de ceux-ci.

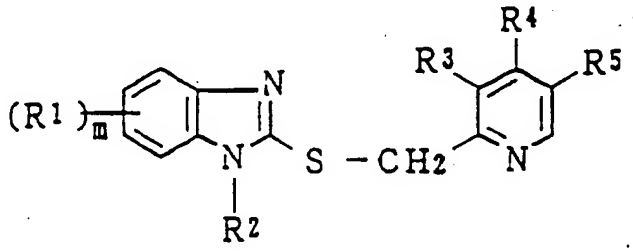
7. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 6, dans laquelle ledit ester d'acide gras de polyglycérol a une valeur HLB (hydrophile-lipophile balance) de 1 à 22.

8. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 7, dans laquelle ledit ester d'acide gras de polyglycérol a un point de fusion de 15 à 80°C.

9. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 7, dans laquelle ledit lipide a un point de fusion de 40 à 120°C.

10. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 9, dans laquelle ladite substance active (i) est un agent antiulcéreux ou un médicament pour le traitement de la gastrite.

11. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 10, dans laquelle ladite substance active (i) est un composé de la formule (II) suivante ou un sel physiologiquement acceptable de celui-ci:



(II)

formule dans laquelle R^1 représente l'hydrogène, un alcoyle, un halogène, un groupe cyano, carboxylique, alcoxycarbonyle, alcoxycarbonylalcoyle, carbamoyle, carbamoylalcoyle, hydroxy, alcoxy, hydroxyalcoyle, trifluorométhyle, acyle, carbamoyloxy, nitro, acyloxy, aryle, aryloxy, alcolythio ou alcoylsulfinyle; R^2 représente l'hydrogène, un groupe alcoyle, acryle, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, alcoylcarbonylméthyle, alcoxycarbonylméthyle ou alcoylsulfonyle, R^3 et R^5 peuvent être identiques ou différents et chacun d'eux représente l'hydrogène, un alcoyle, un alcoxy ou un alcoxyalcoxy; R^4 représente l'hydrogène, un alcoyle, un alcoxy qui peut être fluoré, un alcoxyalcoxy, un alcényloxy qui peut être fluoré, ou un alcynyloxy qui peut être fluoré, et m représente 0 ou un nombre entier de 1 à 4.

12. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 11, dans laquelle R^1, R^2 et R^5, dans ledit composé de formule (II), sont chacun l'hydrogène et R^3 est l'hydrogène ou le méthyle.

13. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 11 ou la revendication 12, dans laquelle R^4, dans ledit composé de formule (II), est un groupe alcoxy fluoré en C_{1-4}.

14. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 11, dans laquelle R^1, dans ledit composé de formule (II), est l'hydrogène, le fluor, le méthoxy ou le trifluorométhyle en tant que substituant de la position 5; R^2 est l'hydrogène, R^3 est l'hydrogène ou le méthyle; R^4 est un alcoxy en C_{1-4} qui peut être fluoré, ou le groupe 2-propényloxy ou allyle; R^5 est l'hydrogène ou le méthyle et m est 1.

15. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 14, qui comprend une base solide insoluble dans l'eau ou peu soluble dans l'eau, ensemble avec une substance active acide.

16. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 14, qui comprend un polymère entérique ensemble avec une substance active basique.

17. Matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 16, dans laquelle la teneur desdites particules de la matrice en ledit ester d'acide gras de polyglycérol et/ou ledit lipide est de 0,001 à 10 000 parties en poids pour une partie en poids de ladite substance active.

18. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 3, dans laquelle la matrice comprend en tant que composant (ii) un ester d'un polyglycérol de formule (I), dans laquelle n est un nombre de 2 à 50, et d'un acide gras supérieur, saturé ou insaturé, comprenant de 8 à 40 atomes de carbone, la teneur en ledit ester d'acide gras de polyglycérol étant de 0,001 à 10 000 parties en poids pour une partie en poids de ladite substance active (i).

19. Matrice adhérant à la muqueuse gastro-intestinale selon la revendication 1, dans laquelle ladite matrice a un point de fusion dans le domaine de 30 à 120°C inclusivement.

20. Préparation pharmaceutique solide comprenant une matrice adhérant à la muqueuse gastro-intestinale selon l'une quelconque des revendications 1 à 19.

21. Composition de revêtement de matrice, destinée à assurer l'adhésion à la muqueuse gastro-intestinale de formes d'administration, à base de matrice, d'une composition pharmaceutique solide, ladite composition de revêtement comprenant (A) au moins un ester d'acide gras de polyglycérol (PGEF) et/ou un lipide choisi parmi les acides gras saturés en C_{14-22} et leurs sels; et (B) au moins un agent de viscosité ayant la propriété de devenir visqueux au contact de l'eau et choisi parmi les polymères d'acide acrylique ayant un poids moléculaire dans le domaine de 1 000 000 à 5 000 000 et contenant de 58,0 à 63,0 pour-cent en poids de groupes carboxyliques, et les sels desdits polymères d'acide acrylique.

22. Composition de revêtement selon la revendication 21, qui contient de 0,005 à 100 pour-cent en poids dudit agent de viscosité (B), calculés d'après la matière non volatile.

23. Utilisation de la composition de revêtement selon la revendication 21 ou la revendication 22, pour revêtir les particules d'une matrice adhérant à la muqueuse gastrio-intestinale selon l'une quelconque des revendications 1 à 20.

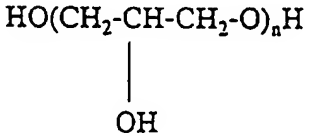
24. Procédé de préparation d'une matrice adhérant à la muqueuse gastro-intestinale, solide à la température ordinaire et qui comprend (i) une substance active; (ii) un ester d'acide gras de polyglycérol et/ou un lipide choisi parmi les acides gras saturés en C_{14-22} et leurs sels; et (iii) un agent de viscosité ayant la propriété de devenir visqueux au contact de l'eau et choisi parmi (a) les polymères d'acide acrylique ayant un poids moléculaire dans le domaine de 1 000 000 à 5 000 000 et contenant de 58,0 à 63,0 pour-cent en poids de groupes carboxyliques, et les sels desdits polymères d'acide acrylique, ledit agent de viscosité étant dispersé dans cette matrice au moins au voisinage de la couche superficielle de chacune des particules de la matrice et, cas échéant, lesdites particules de la matrice comportent une couche de revêtement formée à partir d'une composition de revêtement contenant ledit agent de viscosité, procédé selon lequel

(A) on disperse ladite substance active (i) et ledit agent de viscosité (iii) dans ledit ester d'acide gras de polyglycérol et/ou le lipide (ii), ou (B) on malaxe les composants (i), (ii) et (iii), et

on soumet la masse formée à une granulation,
après quoi, cas échéant, on revêt les granules obtenus de la composition de revêtement contenant ledit agent de viscosité.

25. Procédé selon la revendication 24, dans lequel la teneur en ledit agent de viscosité est de 0,005 à 95 pour-cent en poids par rapport au poids total desdites particules de la matrice.

26. Procédé selon la revendication 24 ou 25, dans lequel ledit ester d'acide gras de polyglycérol est un ester d'un polyglycérol de formule (I):



(I)

dans laquelle n représente le degré de polymérisation, qui est un nombre entier non inférieur à 2, et d'un acide gras supérieur saturé ou insature.

27. Procédé selon la revendication 26, dans lequel n se situe dans le domaine de 2 à 50.

28. Procédé selon la revendication 26 ou 27, dans lequel ledit acide gras est un acide gras supérieur saturé ou insaturé, comportant de 8 à 40 atomes de carbone.

29. Procédé selon l une quelconque des revendications 24 à 28, dans lequel ledit ester d'acide gras de polyglycérol est choisi parmi l'hexa(tétra)glycéride de béhényle, le penta(tétra)glycéride de stéaryle, le mono(tétra)glycéride de stéaryle, le penta(hexa)glycéride de stéaryle, le sesqui(hexa)glycéride de stéaryle, le mono(déca)glycéride de

stéaryle et les mélanges de ceux-ci.

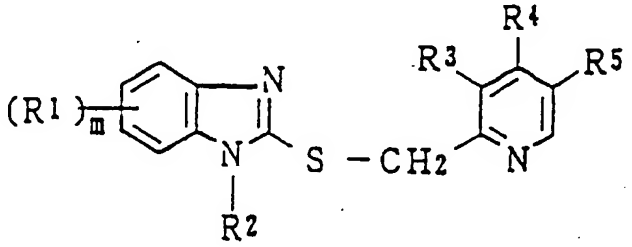
30. Procédé selon l une quelconque des revendications 24 à 29, dans lequel ledit ester d'acide gras de polyglycérol a une valeur HLB (hydrophile-lipophile balance) de 1 à 22.

31. Procédé selon l une quelconque des revendications 24 à 30, dans lequel ledit ester d'acide gras de polyglycérol a un point de fusion de 15 à 80°C.

32. Procédé selon l'une quelconque des revendications 24 à 30, dans lequel ledit lipide a un point de fusion de 40 à 120°C.

33. Procédé selon l'une quelconque des revendications 24 à 32, dans lequel ladite substance active (i) est un agent antiulcéreux ou un médicament pour le traitement de la gastrite.

34. Procédé selon l une quelconque des revendications 24 à 33, dans lequel ladite substance active (i) est un composé répondant à la formule (II) suivante ou un sel physiologiquement acceptable de celui-ci:



(II)

formule dans laquelle R^1 représente l'hydrogène, un alcoyle, un halogène, un groupe cyano, carboxylique, alcoxycarbonyle, alcoxycarbonylalcoyle, carbamoyle, carbamoylalcoyle, hydroxy, alcoxy, hydroxyalcoyle, trifluorométhyle, acyle, carbamoyloxy, nitro, acyloxy, aryle, aryloxy, alcolythio ou alcoylsulfinyle; R^2 représente l'hydrogène, un groupe alcoyle, acryle, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, alcoylcarbonylméthyle, alcoxycarbonylméthyle ou alcoylsulfonyle, R^3 et R^5 peuvent être identiques ou différents et chacun d'eux représente l'hydrogène, un alcoyle, un alcoxy ou un alcoxyalcoxy; R^4 représente l'hydrogène, un alcoyle, un alcoxy qui peut être fluoré, un alcoxyalcoxy, un alcényloxy qui peut être fluoré, ou un alcynyloxy qui peut être fluoré, et m représente 0 ou un nombre entier de 1 à 4.

35. Procédé selon la revendication 34, dans lequel R^1, R^2 et R^5, dans ledit composé de formule (II), sont chacun l'hydrogène et R^3 est l'hydrogène ou le méthyle.

36. Procédé selon la revendication 34 ou 35, dans lequel R^4, dans ledit composé de formule (II), est un groupe alcoxy fluoré en C_{1-4}.

37. Procédé selon la revendication 34, dans lequel R^1, dans ledit composé de formule (II), est l'hydrogène, le fluor, le méthoxy ou le trifluorométhyle en tant que substituant de la position 5; R^2 est l'hydrogène; R^3 est l'hydrogène ou le méthyle; R^4 est un alcoxy en C_{1-4} qui peut être fluoré, ou un groupe 2-propényloxy ou allyle; R^5 est l'hydrogène ou le méthyle et m est le nombre 1.

38. Procédé selon l'une quelconque des revendications 24 à 37, dans lequel la matrice comprend une base solide insoluble dans l'eau ou peu soluble dans l'eau, ensemble avec une substance active acide.

39. Procédé selon l'une quelconque des revendications 24 à 37, dans lequel la matrice comprend un polymère entérique ensemble avec une substance active basique.

40. Procédé selon l'une quelconque des revendications 24 à 39, dans lequel la teneur desdites particules de la matrice en ledit ester d'acide gras de polyglycérol et/ou ledit lipide est de 0,001 à 10 000 parties en poids pour une partie en poids de ladite substance active.

41. Procédé selon la revendication 26, dans lequel la matrice comprend en tant que composant (ii) un ester d'un polyglycérol de formule (I), dans laquelle n est un nombre de 2 à 50, et d'un acide gras supérieur saturé ou insaturé,

comportant de 8 à 40 atomes de carbone, la teneur en ledit ester d'acide gras de polyglycérol étant de 0,001 à 10 000 parties en poids pour une partie en poids de ladite substance active (i).

42. Procédé selon la revendication 24, dans lequel ladite matrice a un point de fusion situé dans le domaine de 30 à 120°C inclusivement.

43. Procédé de fabrication d'une préparation pharmaceutique solide comprenant une matrice adhérant à la muqueuse gastro-intestinale, solide à la température ordinaire et qui comprend (i) une substance active; (ii) un ester d'acide gras de polyglycérol et/ou un lipide choisi parmi les acides gras saturés en C_{14-22} et leurs sels; et (iii) un agent de viscosité ayant la propriété de devenir visqueux au contact de l'eau et choisi parmi (a) les polymères d'acide acrylique ayant un poids moléculaire dans le domaine de 1 000 000 à 5 000 000 et contenant de 58,0 à 63,0 pour-cent en poids de groupes carboxyliques, et les sels desdits polymères d'acide acrylique, ledit agent de viscosité étant dispersé dans cette matrice au moins au voisinage de la couche superficielle de chacune des particules de la matrice et, cas échéant, lesdites particules de la matrice comportent une couche de revêtement formée à partir d'une composition de revêtement contenant ledit agent de viscosité,

procédé selon lequel on soumet ladite matrice à une granulation pour obtenir des granules fins ou des granules, après quoi, cas échéant, on transforme les granules fins ou les granules, par compression, en comprimés ou on remplit des capsules par les granules fins ou par les granules pour obtenir des capsules.

44. Procédé de préparation d'une forme d'administration, à base de matrice, d'une composition pharmaceutique solide adhérant à la muqueuse gastro-intestinale, selon lequel on revêt les particules d'une matrice contenant une substance active d'une composition de revêtement qui comprend (A) au moins un ester d'acide gras de polyglycérol (PGEF) et/ou un lipide choisi parmi les acides gras saturés en C_{14-22} et leurs sels; et (B) au moins un agent de viscosité ayant la propriété de devenir visqueux au contact de l'eau et choisi parmi les polymères d'acide acrylique ayant un poids moléculaire dans le domaine de 1 000 000 à 5 000 000 et contenant de 58,0 à 63,0 pour-cent en poids de groupes carboxyliques, et les sels desdits polymères d'acide acrylique.